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INFLUENZA IN VICTORIA, 1954.[1]

By D. M. McLEAN, J. WHITE and W. J. STEVENSON.

From the Department of Experimental Medicine, University of Melbourne, at the Walter and Eliza Hall Institute of Medical Research, Melbourne, the Fairfield Hospital, Melbourne, and the Victorian State Health Department.

INFLUENZA type A virus has frequently caused epidemics in Victoria. Influenza virus was first isolated in Melbourne in 1935 by Burnet (1935), who designated the strain "Melbourne" (MEL). During an epidemic in June and July, 1939, strains of influenza type A virus were isolated (Burnet and Lush, 1940), and these appeared antigenically similar to MEL. Another large epidemic occurred during May, 1942 (Burnet *et alii*, 1942), and strains of virus isolated were also antigenically similar to MEL. Apart from eight cases which occurred in 1943 (Beveridge and Williams, 1944), no case of influenza was reported in Victoria until September, 1945. During an epidemic caused mainly by type B influenza virus, a strain of type A virus was isolated (MIL-A) which was antigenically distinct from MEL and other type A strains hitherto isolated (Burnet *et alii*, 1946). In May, 1946, a strain of virus CAM, antigenically identical with MIL-A, was isolated during an epidemic (Anderson and Burnet, 1947).

[1] This work was supported in part by a grant from the National Health and Medical Research Council, Canberra.

Epidemics of influenza type A which occurred in the northern hemisphere during January, 1947, were caused by viruses antigenically closely related to CAM. Localized outbreaks of type A influenza occurred in Melbourne in May, 1948 (Anderson, 1948). In May and June, 1950, a large epidemic occurred in Victoria from which the strains A Melb. 1/50 (CHO) and A Melb. 2/50 (PHI) were isolated (Anderson *et alii*, 1953). They were found by Isaacs *et alii* (1952) to resemble closely Liverpool and Scandinavian subtypes of virus which caused large epidemics in England and Europe during January and February, 1951. Another influenza type A epidemic caused by a virus antigenically identical with A Melb. 1/50 occurred in Melbourne in July, 1951 (Anderson *et alii*, 1953).

The present paper reports an epidemic of influenza type A which occurred in Victoria in April, May and June, 1954. The strain of influenza virus responsible, A Melb. 1/54 (FLA), was antigenically distinct from former strains isolated in Melbourne.

Methods and Materials.

The technical procedures were similar to those recorded in earlier papers from these laboratories. Isolation of virus was attempted by inoculation of throat washings into the amniotic cavity of thirteen-day chick embryos (Beveridge and Burnet, 1946) in the presence of penicillin and streptomycin. Influenza virus hæmagglutinin was determined by the pattern test, 1% human group O (IV) and fowl red cells being used. Complement fixation tests

followed the technique of Donnelley (1951), chick embryo lung being used as antigen. Serum was treated with a crude extract of receptor destroying enzyme (RDE) of *Vibrio cholerœ* filtrates and heated at 58° C. for thirty minutes before use in antihæmagglutination tests, according to the method of Isaacs and Bozzo (1951).

The Epidemic.

The first cases of clinical influenza which came to our notice in 1954 were reported from Corryong, a community of about 1000 inhabitants approximately 250 miles north-east of Melbourne. On March 29, 1954, a case clinically resembling influenza occurred, and a blood sample taken fourteen days later contained a high titre of antibody to type A influenza as determined by complement fixation (CF) and antihæmagglutination (AHA) tests. A total of 35 cases was dealt with by one of us (W.J.S.). The majority of cases occurred during the weeks ended April 3 and April 10, and the last case occurred on April 25.

Specimens of serum were obtained from 29 of the patients. Twenty-three of these were taken six or more days after the onset of illness, and these were considered as convalescent sera. In the remaining six patients an acute serum was obtained less than six days after the onset of illness, and a convalescent serum was obtained about a fortnight later. Twenty of the 23 specimens of convalescent serum contained CF antibody at a titre greater than 20 and/or AHA antibody to strain A Melb. 1/54 (FLA) at a titre greater than 20. Three of the six pairs of sera showed a fourfold or greater increase in CF and AHA antibody titre in the second serum sample (Table I). Unsuccessful attempts at virus isolation were made in two of the three cases in which a rising titre of influenza antibody was detected. There was no serological evidence that any case was caused by influenza type B.

An attempt was made to isolate influenza virus from the throat washings of six patients examined between twenty-four and forty-eight hours after the onset of symptoms. From three washings a type A influenza virus was isolated, and the strain A Melb. 1/54 was selected as representative of the group for more detailed study. It was unfortunate that second specimens of serum were not obtained from the three patients who had virus in their throat washings.

TABLE I.
Laboratory Findings in Corryong Cases.

Subjects.	Virus Isolation.	Pairs of Serum.	Convalescent Serum Only.
Number giving positive results	3	3[1]	20[2]
Number tested	6	6	23

[1] Fourfold or greater rise in CF and/or AHA antibody in convalescent serum.
[2] CF titre >20 and/or AHA titre >20.

From the results presented in Table I there appears to be little doubt that the influenza virus strain A Melb. 1/54 was responsible for the epidemic of influenza in Corryong in March and April, 1954.

In Melbourne, the first clinical case of influenza dealt with by one of us (D.M.M.) occurred on May 1 in a member of the nursing staff of a large public hospital. A total of 13 cases occurred among the nursing staff, and the last case occurred on June 7. Clinical cases of influenza occurred in a boys' boarding school 40 miles south-west of Melbourne during the first and second weeks of May. This school was visited on May 10, and throat washings were taken from six boys who had developed symptoms during the previous twenty-four hours. Between May 1 and June 15, approximately 8% of troops stationed at an army camp 60 miles north of Melbourne were admitted to the camp hospital with upper respiratory tract infection, probably influenza. A total of 36 men were examined by us during visits on May 5 and 8, and further blood samples were obtained from these men on May 27. Very few cases were reported in the camp during the week preceding June 16, and on this date we obtained blood samples from 33 volunteers who had not suffered from colds or clinical influenza during the previous three months.

The clinical cases were of moderate severity; no seriously ill patient was seen. Headache and lassitude were followed in a few hours by fever, and subsequently by aches and pains in the back and legs. Symptoms usually persisted for three or four days, and the average period off duty was approximately five days.

Electrocardiograms were taken from 12 nurses within forty-eight hours of the onset of symptoms, and again two to three weeks later. Leads I, II, III, V_2, V_4, V_6 were recorded. We are indebted to Dr. M. J. Etheridge, who reported on the tracings. No abnormality was detected in any of the electrocardiograms. Nine of the 12 patients developed serological evidence of recent infection with influenza type A.

Type A influenza virus, antigenically identical with A Melb. 1/54, was isolated from 16 throat washings out of 37 tested from all these situations. A fourfold or greater increase in CF and/or AHA antibody to influenza type A was demonstrated in 50 pairs of serum out of 55 examined (Table II).

TABLE II.
Laboratory Findings in Cases Near Melbourne.

Subjects.	Virus Isolation.	Serum Pairs from Clinical Cases.	Serum from Healthy Volunteers.
Number giving positive results	16	50[1]	8[2]
Number tested	37	55	34

[1] Fourfold or greater rise in CF and/or AHA antibody in convalescent serum.
[2] CF titre >10.

Of the 34 asymptomatic volunteers in the army camp, eight had antibody to type A complement fixing antigen. Since this antibody does not normally persist for more than six to nine months after infection, we assume that it was produced as a result of subclinical infection with type A influenza virus during the 1954 epidemic. Fifteen volunteers suffered from one or more colds, but not clinical influenza, during April and May, 1954, and seven of these had antibody to type A influenza antigen. If we assume that this sample is representative of the camp population, we infer that 24% of those who did not have any symptoms received a subclinical infection with influenza virus. Thus the ratio of cases to subclinical infection was 1:3.

In a group of 1000 employees of a large undertaking in Melbourne, more than twice as many people were absent from work with upper respiratory tract infections during each week of May, 1954, than in the corresponding period in 1953, when clinical influenza was not recognized. From the week beginning June 4, 1954, the average absentee rate fell to that of the corresponding period in 1953, and this correlated fairly well with the virtual absence of clinical influenza as reported from other sources after that date.

We conclude that strains of type A influenza virus antigenically resembling A Melb. 1/54 caused a widespread epidemic of influenza in Melbourne and nearby centres during May and early June, 1954. Cases of influenza probably occurred in Melbourne during April, when the Corryong epidemic was at its height, but an epidemic did not occur in Melbourne until three to four weeks after it was reported in Corryong.

The Virus.

Seven strains of virus which have been examined closely appeared identical serologically. The strain A Melb. 1/54 was used for comparison with previously isolated strains. The results of AHA titrations on both human serum from

TABLE III.

Serological Comparison of A Melb. 1/54 with Standard Type A Strains.

Strain of Virus Hæmagglutinin.	AHA Titre of Ferret Serum Prepared Against Virus			AHA Titre of Three Pairs of Human Serum 1954.		
	A Melb. 1/54.	A Melb. 1/50.	CAM (1946).			
A. Melb. 1/54	20–1280[1]	<10–80	– 60	<10–480	<10–200	<10– 800
A. Melb. 1/50	30– 15	<10–480	– 20	<10– 35	<10–160	<10– 240
CAM (1946)	<10– 40	40–100	–320	25– 50	<10–560	15–>1280

[1] Ferret serum taken before inoculation and two weeks after intranasal inoculation.

the present epidemic and ferret serum prepared against each of the three virus strains are shown in Table III.

It is evident that A Melb. 1/54 differs antigenically from strains isolated during former epidemics in Melbourne. There appears to be a slight antigenic overlap between CAM (Melbourne, 1946) and A Melb., 1/54, to a greater extent than between A Melb. 1/50 and A Melb. 1/54. Ferret sera showed a rise in antibody titre to a greater extent against the homologous virus than against the heterologous (strain-specific response), but 17 human sera out of 19 tested showed considerable antibody response to all three strains of virus (broad response).

Representative strains of virus (A Melb. 1/54 and A Melb. 2/54) were sent to Dr. A. Isaacs at the World Influenza Centre. He reported that they bore a close antigenic relationship to the strains A England 1/53 and A Netherlands 1/53, which were isolated from subjects of influenza early in 1953 (Isaacs, personal communication). This has been confirmed in these laboratories in the case of A Melb. 1/54, A Melb. 2/54 and A England 1/53.

The virus, when first isolated by amniotic inoculation of chick embryos, was found to be in either the O-phase or a phase intermediate between O and D (Burnet and Bull, 1943). On further passage of low dilutions (10^{-1} or 10^{-2}) of amniotic fluid, D-phase mutants were recovered from O-phase stock. The virus was then cultivated readily in the allantoic cavity. When more dilute inocula (10^{-4} or 10^{-5}) were used for passage, O-phase virus was recovered consistently.

Summary.

An epidemic caused by type A influenza virus occurred in Victoria during April, May and June, 1954. The strains of virus isolated differed antigenically from strains previously isolated in Victoria, but resembled closely A England 1/53 isolated in England in 1953.

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We wish to acknowledge gratefully the assistance given by Dr. S. G. Anderson, Dr. M. J. Etheridge, Dr. R. F. F. Harbison, Mr. J. Lawrence, Dr. B. L. Marks, Dr. D. Metcalf, Dr. V. G. Renowden and Dr. M. G. Williams. We are particularly grateful to the following officers of the Royal Australian Army Medical Corps: Colonel J. G. White, Major A. P. Hanway and Captain L. Atkinson.

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A MEASURE OF METABOLIC AGE.[1]

By R. L. WORRALL, M.B., Ch.M., D.P.H.,
Sevenoaks, Kent, England.

GROWTH and aging are two aspects of biological development. Growth of an organism involves increase of its mass (W) and also increase of its potential energy (E), measurable in Calories by means of a bomb calorimeter, and sometimes called "calorific value". The following communication indicates that the metabolic aging of an organism is measurable in terms of increase of its energy-mass ratio (E/W).

Post-mortem measurements of eight human infants (Camerer and Soldner, 1900-1903; Shohl, 1939) and of one adult (Mitchell, 1945) show a rapid increase in the value of the energy-mass ratio during embryonic life, and a much slower increase during post-natal life. From these measurements the following figures for E/W are obtained: Five months' fœtus, 445 Calories per kilogram of body weight; seven months' fœtus, 745 Calories per kilogram of body weight; newborn infant (average of six), 1851 Calories per kilogram of body weight; male adult (thirty-five years), 1930 Calories per kilogram of body weight.

The figures for Calories represent the energy value per kilogram of body weight of body fat (9·3 Calories per gramme) *plus* body protein (4·1 Calories per gramme). No figure is available for the comparatively small amount of carbohydrate in the human body.

Jean Mayer and others have shown that increase of weight in an adult organism represents a much greater increase of potential energy than the same increase of weight in a young organism. If the weight of an adult animal increases by five grammes through the addition of fat, the energy increase is about ten times that of a young animal whose weight increases by the same amount, through the addition of one gramme of protein and four grammes of water and minerals (Mayer, 1949).

In the case of a normal adult who is in nitrogen equilibrium, and whose protein content therefore remains unchanged, increase of potential energy per unit weight occurs through one or more of the following processes:

[1] Abstract of research project presented at the Research Committee Section of the Third Congress of the International Association of Gerontology, London, July 20, 1954.

1. Addition of fat. In the case of a normal human adult weighing 70 kilograms, whose potential energy is 1930 Calories per kilogram, addition of one kilogram of fat increases the energy-mass ratio by 5·4%, if body water and bone mineral remain unchanged.

2. Depletion of water. If the body water of the 70-kilogram adult decreases by one kilogram, with no other change in the overall composition of the body, the energy-mass ratio increases by 1·44%. If, however, one kilogram of added fat displaces one kilogram of body water, the energy-mass ratio increases by 6·88%.

3. Demineralization of bone. Bone mineral, whose energy value is zero, has a density of 2·9 to 3·0, and comprises about 4% of adult body weight (Keys *et alii*, 1950). A loss of one kilogram of bone mineral increases the energy-mass ratio of the 70-kilogram adult by 1·44%, if there is no other change in the overall composition of the body.

All the foregoing processes occur in aging of animals. The research project proposed is post-mortem measurement of the energy-mass ratio of small animals, by means of a bomb calorimeter, in order to determine changes in the value of that ratio for the whole animal, with chronological age.

If the value of the energy-mass ratio is taken as a measure of metabolic age, growth and aging can be related numerically. Generally speaking, growth of a human individual as a whole does not occur after the individual's energy-mass ratio reaches a critical value of the order of 1930 Calories per kilogram, on attainment of maximum stature at the age of eighteen or nineteen years.

At the beginning of an individual's existence, at the time of fertilization of the ovum, the growth rate is also zero. It might be expected, therefore, that the human ovum, at the commencement of its development into an embryo, would have a high energy-mass ratio associated with a low water content. The available evidence supports this view.

The fertilized human ovum, according to C. B. Davenport (1937), absorbs a relatively large amount of water during its early development into an embryo, "until, after six weeks, the egg is nearly 98 per cent water. By this means the egg comes to weigh about a gram, or nearly 500,000 times its initial weight, the increase being mostly water."

This means that the energy-mass ratio of the six weeks' human embryo must be lower than 186 (the value of the ratio if the embryo's non-aqueous 2% consisted entirely of fat). Davenport's estimate implies a much higher value of the energy-mass ratio of the ovum at the time of fertilization, before the rapid hydration associated with earliest development.

During an individual's earliest development, immediately after fertilization of the ovum, when hydration is taking place and the value of the energy-mass ratio is therefore declining, the growth rate must rise for a time, since it is zero at the time of fertilization. Soon, however, the degree of hydration of the developing embryo begins its well-known decrease, the energy-mass ratio begins its long climb towards a high value of adult life, and the rate of growth begins to fall.

With cessation of growth of the individual as a whole, at the age of eighteen or nineteen years, further increase of the energy-mass ratio can occur through increase of fat at the expense of body water, and such an increase apparently underlies typical signs of tissue degeneration in the adult phase of aging.

The pendulum swing in the value of the energy-mass ratio, from a high value for the ovum to a high value for the adult, is indicated by the figures shown in Table I, obtained from data presented by Needham (1931).

This approach to problems of aging permits a comprehensive interpretation of changes in enzyme activity with chronological age. Of the mass of the adult human body, 90% is that of carbon, hydrogen and oxygen atoms. Over 90% of the hydrogen atoms of the body are attached to either carbon or oxygen. Hydrogen attached to carbon represents mass, and also the potential energy which constitutes calorific value. Hydrogen attached to oxygen represents mass, but not the potential energy which constitutes calorific value. For any cell, tissue or organism, therefore, the value of the energy-mass ratio is a function of the proportion of total carbon-hydrogen bonds to total oxygen-hydrogen bonds, and this proportion depends in turn on the pattern of enzyme activity of the cell, tissue or organism. Changes in the pattern of enzyme activity with the onset of old age can thus be interpreted with reference to the tendency of the energy-mass ratio to increase or decrease towards a limit.

TABLE I.

The Energy-Mass Ratio, in Calories per Kilogram of Wet Weight.

Animal.	Egg (Unincubated).	Embryo at Some Time After Commencement of Incubation of Egg.	Adult.
Silkworm	2163	1632 (Fifteenth day)	—
Hawk moth ..	—	709 (" Larva.")	1376 (" Imago.")
Frog	1627	550 (Twentieth day.)	—

During senescence, when cell degeneration is a typical feature of aging, solid tissues may become more hydrated, owing to reduction of cell solids relative to extracellular water. It is possible, therefore, that the energy-mass ratio of an animal organism as a whole may fall in value during senescence. That is to say, the organism's metabolic age may tend towards an earlier and lower level with the onset of old age. This does not alter the fact that the cell degeneration of senescence increases the energy-mass ratio of most of the cells of the body until they can no longer support the life of the organism as a whole.

The commonest forms of the cell degeneration of senescence are cell atrophy and fatty degeneration of individual cells. In cell atrophy, cells become smaller and denser, their increasing proportion of total organic solids to intracellular water being evident in deeper staining of such cells. In fatty degeneration the increasing proportion of total organic solids to intracellular water is indicated by visible accumulation of fat in the cytoplasm. In both forms of degeneration the increased proportion of total organic solids to intracellular water represents an increased value of the energy-mass ratio of the cells, as distinct from whole tissues and the organism as a whole.

Individual cells, however, depend for their metabolic age on the composition and circulation of the blood. The prediction is here made that whole blood during senescence will show a rise in the value of its energy-mass ratio.

By the use of the energy-mass ratio as a measure of metabolic age it is also possible to correlate problems of differentiation with those of growth and aging. Differentiation is essentially an approach towards invariance of specific relations of a biological system, and it is seen while the energy-mass ratio of that system is increasing towards a limit. Each set of relations becomes invariant as the energy-mass ratio reaches a particular value. Specific relations of the human fingerprint pattern, for example, become invariant between the third and fourth months of embryonic life (Cummins, 1946), at which time the energy-mass ratio of the embryo as a whole reaches a value of 246, according to figures presented by Shohl (1939).

The relationship between biological differentiation and potential energy change is covered by the following general law of open systems: in an open system with feedback, specific relations of the system approach invariance, as the potential energy of the system tends towards a limit. In a living cell the chains of feedback include connexions between batteries of enzymes, permitting adaptation of the cell to environmental changes. The foregoing law, here termed the regulating principle, can be expressed mathe-

matically as follows: the limit of p as m approaches n is q, where p is the potential energy of an open system with feedback, q is a limit of p, m is a specific relation of the system, and n represents that relation when it is invariant.

Summary.

A living organism is an energy trap. The "driving force" of growth and aging is the tendency of living organisms to accumulate energy. Cell division, cell differentiation and cell degeneration are based upon changes in the value of the energy-mass ratio of the cell.

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THE FŒTAL AND NEONATAL WASTAGE DUE TO SENSITIZATION BY THE Rh FACTOR

By G. A. KELSALL AND G. H. VOS,

The King Edward Memorial Hospital for Women, Perth.

FOR several years we have been curious to determine whether immunization in pregnancy indeed contributes as large a number of deaths to the general fœtal and neonatal wastage as one's clinical impression would lead one to believe. In itself, hæmolytic disease in a newborn infant is rare, but many infants may not survive even to be born alive. It is only when serological work is performed in ante-natal cases at frequent intervals that one becomes aware of the number of infants which fall by the wayside long before full term has been achieved.

Walsh (1945) and de Burgh *et alii* (1947) have shown that Rhesus incompatibility does not *per se* lead to an increase in the number of abortions in Rh-negative women. When our figures for the strongly immunized mothers were first examined, we had formed the impression that the miscarriage rate in such women was considerably increased.

We have had the opportunity in the last four years to observe 260 mothers in whose serum Rhesus antibodies have been detected on at least one occasion. We have now analysed these cases to determine the over-all childbearing wastage occasioned by Rhesus incompatibility. The three main questions which we have attempted to solve have been the following: (i) Does immunization by the Rh factor cause abortions? (ii) Is it responsible for a large number of stillbirths? (iii) What is the total fœtal and neonatal wastage? The third question is difficult to answer with any great degree of accuracy, because many of the mothers have been treated when necessary by premature induction of labour and the infants by exchange transfusion; this possibly gives a favourable bias to the figures when compared to cases in which no treatment has been given.

In each instance the total number of pregnancies has been taken into account. Some of the mothers had their first baby as early as 1935, but the majority of the pregnancies occurred within the period from 1940 to 1950, while our observations upon the women were made between 1950 and 1954. Their histories were elicited by one of us personally.

The serological work has been done exclusively in the hospital laboratory. The titrations have been by the standardized indirect Coombs method as described previously (Kelsall and Vos, 1952; see Appendix I). The mothers have been placed in the various categories (Table I) according to the highest titration figure observed while they were under our care. It should be pointed out that our highest observed titre may not necessarily have been the highest titre which that particular mother may have experienced. It may have been higher on some other occasion when she was not under our care.

The control group was provided by the random selection from the records of the clinic of patients having had children in the hospital during 1952 and 1953. It has been assumed that the Rh-positive women chosen as controls have not been immunized, and that their pregnancies have been compatible. We are aware that Rh subtype or "other-factor" immunization may have occurred, but the incidence must be extremely small. The records of two Rh-positive women were taken for every one immunized Rh-negative woman, the records being matched for the mother's age, A B O group and number of pregnancies. The control group, double that of the experimental group, was thus directly comparable except for closeness of questioning with respect to previous pregnancies. These histories were taken by other members of the hospital staff. It is likely, then, that the frequency of miscarriages is understated in the controls, since it is sometimes difficult to obtain the unsolicited admission of a miscarriage, because many mothers tend to "forget" such an occurrence even when asked the direct question. The survival time for children of both immunized and control women was taken as fourteen days, since the infants of the controls were not observed again after they had left hospital.

If immunization is responsible for an increased wastage, is it in any way related to the strength of antibody titre? The mothers were therefore classified according to the highest observed titre into three groups: (i) those with titres below 1:128, (ii) those of titres 1:128, 1:256 and 1:512; and (iii) those with titres of 1:1024 or higher.

Statistical analysis of the control groups (i), (ii) and (iii) showed that there was no significant variation between the groups and that they were homogeneous ($\chi^2 = 2{\cdot}795$ for six degrees of freedom; $0{\cdot}9 > P > 0{\cdot}8$), so that the means and totals for the whole control series have been used rather than the controls in groups (i), (ii) and (iii) for subsequent calculations. A similar test among the Rh-negative patients shows a highly significant heterogeneity ($\chi^2 = 88{\cdot}404$; $P \ll 0{\cdot}001$).

Results.

There is no significant difference between the miscarriage rate for Rh-negative women in group (i) and that of the controls ($\chi^2 = 2{\cdot}7$ for one degree of freedom, $P = 0{\cdot}1$), while the apparent rise in the miscarriage rate between group (i) and group (iii) is also not significant ($\chi^2 = 1{\cdot}358$ for two degrees of freedom, $P \sim 0{\cdot}5$).

If it is borne in mind that the miscarriages among controls are probably understated, it is clear that Rh immunization, even at high antibody levels, does not appreciably increase the miscarriage rate.

The combined stillbirth and neonatal death rates in group (i) just fail to attain significance when tested against the controls ($\chi^2 = 3{\cdot}195$ for one degree of freedom; $0{\cdot}10 > P > 0{\cdot}05$).

The combined stillbirth and neonatal death rates for group (ii), however, is significantly different from the controls ($\chi^2 = 35{\cdot}39$; $P \ll 0{\cdot}001$) and also the rates for group (iii) ($\chi^2 = 56{\cdot}85$; $P \ll 0{\cdot}001$).

TABLE I.

Group.	Immunized Rh-negative Mothers.							Controls: Rh-positive Mothers Individually Matched for Number of Pregnancies, Age and A B O Group.						
	Maternal Indirect Coombs Titre.	Number of Mothers.	Number of Fœtuses.	Number of Miscarriages.	Number of Stillbirths.	Number of Neonatal Deaths.	Survival Rate at Fourteen Days.	Number of Mothers.	Number of Fœtuses.	Number of Miscarriages.	Number of Stillbirths.	Number of Neonatal Deaths.	Survival Rate at Fourteen Days.	Average Number of Fœtuses per Family.
(i)	Less than 1 : 128 ..	40	161 (100%)	11 (6·83%)	5 (3·10%)	5 (3·10%)	140 (86·96%)	80	322	17	7	7	291	4·025
(ii)	1:128, 1:256, 1: 512	111 (10·0%)	414 (100%)	37 (8·94%)	27 (6·52%)	16 (3·86%)	334 (80·68%)	222	828	33	13	17	765	3·73
(iii)	1 : 1024 or higher ..	109	434 (100%)	43 (9·91%)	81 (18·66%)	56 (12·90%)	254 (58·33%)	218	868	32	14	14	806	3·98
	All titres ..	260	1009 (100%)	91 (9·02%)	113 (11·20%)	77 (7·63%)	728 (72·15%)	520	2018 (100%)	82 (4·07%)	34 (1·69%)	38 (1·88%)	1862 (92·36%)	3·88

These findings would indicate a highly significant correlation between the maternal antibody titre and the stillbirth and neonatal mortality rates, but not between the maternal antibody titre and the miscarriage rate.

Conclusions.

It would seem unlikely that iso-immunization is responsible for many abortions, no matter how high the maternal antibody titre. Nor are stillbirths likely to occur when the antibody titre is low. We have other evidence that an antibody titre of 1:128 would appear to be a critical figure, and this is supported by the present study. Mothers whose antibody titres are above this figure have an increased number of stillbirths, and if their infants are born alive, an increased number of neonatal deaths. The combined stillbirths and neonatal deaths in all the immunized subjects amounts to 18·83%, as compared to 3·57% in the controls.

Since stillbirths are counted from the twenty-eighth week of gestation or later, it appears that the results of immunization are maximal in the latter part of pregnancy. The figures show that more losses occur as stillbirths than as neonatal deaths, but it must be remembered that a proportion of the live-born infants may have been retrieved by premature induction of labour and transfusion therapy. The survival rate for the immunized subjects at fourteen days when the infants left hospital in good health with their mothers was 72·15% (of 1009 fœtuses), while it was 92·36% (of 2018 fœtuses) in the non-immunized control series. The percentage wastage due to immunization in these cases may therefore be taken as the difference between the two figures—namely, 20%.

The emphasis is now upon stillbirths. Since their number is higher than that of neonatal deaths among the immunized subjects, the point of attack against hæmolytic disease of the newborn should be directed against the stillbirths. A partly effective means is by premature induction of labour and exchange transfusion, but there seems to be no effective way at present of saving the infants of mothers who become strongly immunized before the completion of thirty-six weeks of gestation.

Summary.

Figures for miscarriages, stillbirths and neonatal deaths were obtained from a study of 260 immunized Rh-negative mothers, who had a total of 1009 fœtuses. They were compared with 520 Rh-positive mothers of the same age, number of pregnancies and A B O blood group, who had a total of 2018 fœtuses, each Rh-negative woman being individually matched with two Rh-positive women in the above-mentioned respects.

Statistical analysis gave the following results.

1. With the small number of cases available for analysis, immunization by the Rh factor does not lead to a significantly increased number of abortions.

2. On the other hand, immunization leads to a greatly increased number of stillbirths, and the higher the antibody titre, as measured by a standardized indirect Coombs titration, the higher the percentage of stillbirths.

3. Hæmolytic disease of the newborn has its greatest impact upon the fœtus in the last trimester of pregnancy, and upon the newborn infant. Expressed as survivals, the percentage of infants alive and well fourteen days after delivery in the affected series was 72·15, while 92·3 of the controls survived. The greatest losses occasioned by the disease occurred as stillbirths, but this is probably influenced by the fact that many of the newborn babies were treated, and possibly survived, as a result of exchange transfusion. Many potential stillbirths may have been avoided by premature induction of labour.

4. The figures indicate a highly significant positive correlation between the indirect Coombs titration of maternal antibodies and the combined stillbirth and neonatal mortality rates.

Acknowledgements.

We wish to express our thanks to Mr. R. L. Kirk and Mr. J. W. Shield for the statistical analyses and to Miss P. M. Piesse for help in collecting the material. Without their help these figures would indeed have had little meaning.

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Appendix: Technique of the Antiglobulin Titration.

The specifically reactive test cells (usually group O CDe/CDe and group O CDe/cDE cells) are washed three times in normal saline, then made up to a 10% solution in normal saline. The washing is a most important procedure and on no account may be omitted.

Place 0·4 millilitre of the undiluted serum to be tested in the first and second serial test tubes. In the second and each succeeding tube place 0·4 millilitre of normal saline. Then prepare serial dilutions in the usual manner by transferring 0·4 millilitre of the serum saline solution to each succeeding tube, starting from the second tube. Discard 0·4 millilitre from the final tube. To each tube add 0·4 milli-

litre of the above-mentioned 10% cell suspension. Then place the tubes in the water bath at 37° C. for one hour. (We have adopted the convention of calling the first tube "one in two" and not "full strength". Our titration results are therefore one dilution higher than they would be had we called the first tube "full strength" or "one in one".)

Wash the cells three times, using 10 volumes of normal saline solution, then remove the saline.

Add normal saline to two and a half times the volume of cells, thus giving a 40% cell suspension.

Place a drop of this cell suspension from each tube on a slide and add one drop of Coombs reagent (Commonwealth Serum Laboratories) to each. The reagent is used according to the directions. We have found it to be specific, sensitive and uniform from batch to batch.

Gently tilt the slide from time to time and read the results in six minutes and not longer than ten minutes at room temperature.

Note at which dilution agglutination is just present as read by the naked eye. The reciprocal of the dilution is taken as the titre.

Rhesus-negative (group O cde/cde) control cells are used in parallel with the test cells.

REACTIONS TO THE INJECTION OF CONCENTRATED TUBERCULIN.

By ELLIS ABRAHAMS, M.D., M.R.C.P.,
Director of Tuberculosis, Queensland,
AND
JOHN FRANCIS, M.Sc., M.R.C.V.S.,
Professor of Preventive Medicine, Veterinary School, University of Queensland.

THE intracutaneous injection of tuberculin is one of the commonest biological tests performed on both man and animals, and there is considerable literature upon the subject. Tuberculosis has reached a high incidence in cattle in many parts of the world and, as in man, occurs even under the most favourable environmental conditions. In the early attempts to control the disease clinical and bacteriological methods were used, as it was deemed impracticable to remove all animals that reacted to the tuberculin test. This was done partly as a public health measure, and partly because it was hoped that removal of infected animals would reduce the incidence of tuberculosis in cattle. The number of severe clinical cases was undoubtedly much reduced, but there was little effect on the total incidence of tuberculosis, even in Germany where special methods were employed to obtain tracheal mucus and the programme was carried out with characteristic thoroughness (Francis, 1947). The tuberculin test has formed the basis of all successful schemes for the control of tuberculosis in cattle, and the disease has been virtually eradicated from the United States of America and some other parts of the world (Francis, 1950). The progress in Australia has been presented by Seddon (1953).

In cattle in Australia tuberculin is injected into one of the caudal folds; these are the folds of skin ventral to the tail on either side of the anus. In some other countries injection is made into the skin of the neck; but whichever route is used, it is not surprising that sudden movement of the animal may lead to accidental injection of tuberculin into the finger or thumb of the operator. As undiluted old tuberculin, or P.P.D. tuberculin of corresponding strength (Gregory, 1949) is used in veterinary practice, it is not surprising that severe reactions may result. Some 250,000,000 cattle were tuberculin tested in the United States of America between 1917 and 1945, and enormous numbers have been tested in other parts of the world; but so far as we are aware, the effects of the accidental injection of concentrated tuberculin into man have not been described.

A recent experience of one of us (J.F.) having most pointedly brought the subject to our attention, inquiry disclosed that, although most veterinary surgeons are familiar with the condition, few medical practitioners are acquainted with it. As the symptoms and signs may closely simulate a pulp-space infection, an inquiry into some features of the condition was undertaken.

A *questionnaire* was issued to most veterinary surgeons in Australia. The general symptoms of each patient were given a score of 0 to 11, this score being the sum of the individual scores for the degree of fever, malaise, rigor and headache. The local reactions of each patient were given a score of 0 to 12, depending upon the degree of pain, swelling, discoloration, necrosis or desquamation, and upon the time elapsing before recovery.

Results.

The answers to the *questionnaire* showed that accidental injections were very common, for in spite of one comment that "extreme clumsiness would be necessary to ever have this accident occur", 127 out of 172 veterinary surgeons who replied to the *questionnaire* (74·4%) had once or more than once injected some part of their, or an assistant's, anatomy. Moreover, of those who had not done so, many said they did little tuberculin testing.

Scores showing the severity of local and general reactions are given in Table I, and it will be seen that there was great variation in the response. There was no local reaction in 28 instances; the reaction was mild (score of 1 to 4) in 66, moderate (score of 5 to 8) in 28, and severe (9 to 11) in 11. General reactions were much less frequent, and none was recorded in 97 cases; 11 others were mild (scores of 1 to 2), 15 were moderate (scores of 3 to 6), and four were severe (scores greater than 6).

TABLE I.
Severity of Reactions to Accidental Injection of Tuberculin in 127 Patients.

Score.[1]	Local Reactions.	General Reactions.
0	28	97
1	7	7
2	13	4
3	19	6
4	21	2
5	10	5
6	8	2
7	3	1
8	7	1
9	6	0
10	3	2
11	1	0
12 and over..	1	—

[1] See text for method of scoring.

In the most severe reaction a rise of temperature up to 104° F., with malaise and a severe headache, developed some nine hours after the injection, and persisted for thirty-six hours. During this period the patient experienced a typical rigor. The injection site (pulp of thumb) became intensely painful and swollen, red and subsequently purple in colour. The pain and swelling were severe for three days and then gradually subsided. Numbness persisted for some two or three weeks before the thumb returned to normal. This patient commented: "If there is no infection, the patient must adopt a philosophical attitude, knowing that subsidence of symptoms and complete recovery is only a matter of a short time."

The experience of one of us may be taken as typical of a fairly severe local reaction, which was given a score of 9.

About 0·01 cubic centimetre of undiluted Commonwealth Serum Laboratories synthetic-medium tuberculin was injected subcutaneously into the pulp of the left thumb during tuberculin testing of a horse. There was a stinging pain in the thumb about three hours later, and after ten hours the thumb began to swell and was tender to touch. Symptoms increased in severity and were unrelieved by hot or cold bathing. The swelling continued, and after forty-eight hours the thumb was red, hot, swollen, tense and tender over the pulp and, to a lesser extent, the distal third of the

proximal phalanx. About the site of the needle puncture the skin was œdematous, and whitened readily on light pressure. There was no lymphangitis and the regional lymph nodes were not enlarged. The temperature was normal.

The appearances were indistinguishable from a pulp-space infection, a finding confirmed in consultation with Dr. A. R. Murray. However, as the patient had been vaccinated with B.C.G. four years previously, and was known to react to one one-thousandth of a milligramme of old tuberculin, it was thought most probable that the reaction was, in fact, a tuberculin reaction, and that the severe throbbing pain, which was the outstanding clinical feature, was due to the anatomy of the pulp-space. Because of this, incision which would certainly have been indicated in a coccal infection of similar severity was not undertaken. Procaine penicillin was given for three days, as the possibility of infection could not be excluded, but it appeared to have no effect. Aspirin, in a dosage of 20 grains every four hours, gave considerable relief. Local swelling and redness were maximal at forty-eight to seventy-two hours, then slowly subsided; but it was ten days before the thumb was entirely normal.

Points of interest from answers to the *questionnaire* were the occurrence of local necrosis with subsequent desquamation, and the great variety of injection sites which the struggles of the animals being tested produced, varying from the point of the chin, the wrist, the arm of an assistant, to the foot of the injector. However, the great majority of injection sites were in the thumb or fingers of the hand pinching up the skin fold, the pulp of either finger or thumb being the commonest site. In addition to injection, several replies mentioned the splashing or spraying of tuberculin into the eyes. This, in some sensitive individuals, produced a typical ocular tuberculin reaction, and one man at least was more worried by this than by injecting his finger.

In some subjects repeated injections produced less severe reactions, and in others more severe reactions. Possibly the dosage and time intervals are important in this regard, frequent small injections being likely to produce desensitization, as in the tuberculin treatment of human tuberculosis.

The pulp space was incised once, and incision was contemplated several times by medical practitioners consulted. Antibiotics were administered several times.

Discussion.

There is no precise evidence of the allergic status of the various subjects, but man develops a much greater hypersensitivity to tuberculin than other animals, and there can be little doubt that the reactions described were tuberculin reactions, and that their severity depended partly on the allergic status of the subject and partly on the local anatomy of the digital pulp.

Expectant treatment is advised for this condition. The administration of aspirin in large doses (20 to 30 grains every four hours) gives considerable relief, and morphine should not be withheld if the pain is severe. Incision is rarely indicated, as in only one case was there evidence of infection. The solution injected is sterile, and though the needle itself is soiled with use, the fluid probably remains uncontaminated. If there is any doubt on this point, antibiotic "cover" may be indicated.

Summary.

1. Replies to a *questionnaire* were received from 172 veterinary surgeons, of whom 127 had accidentally injected themselves on one or more occasions with the concentrated tuberculin used for testing cattle.

2. Four persons had severe general reactions, but 97 had none. Eleven persons had severe local reactions and 28 none. The local reactions simulated a pulp-space infection and took six to twelve days to subside.

3. Aspirin often caused considerable relief from pain, but morphine was required occasionally.

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A REVIEW OF THE FACTORS INVOLVED IN THE SUCCESSFUL ADMINISTRATION OF TRICHLORETHYLENE.

By WILLIAM H. J. COLE, D.A.,
Melbourne.

THE anæsthetic agent trichlorethylene is a very valuable one which the writer believes is not used as frequently as it deserves to be because of certain difficulties in administration. The aim of this paper is to discuss these difficulties without attempting to exhaust the subject of trichlorethylene anæsthesia.

The principal difficulties in the administration of trichlorethylene are those of slow induction of anæsthesia, slow recovery, the development of tachypnœa and tachycardia, the problem of chemical instability, and certain difficulties of maintenance. These will now be considered in detail.

The Problem of Slow Induction.

The vapour of the pure forms of trichlorethylene now in use is to some extent irritating to the lungs, and as a result the concentration which can satisfactorily be presented to the patient is often limited by his tendency to cough. If one were to induce anæsthesia by the use of trichlorethylene only, the induction period would be prolonged, although it is a satisfactory method which does not appear to worry patients unduly. In general it is better to commence induction with a more quickly acting agent, and to follow this by trichlorethylene. The following methods have been satisfactory:

1. The intermittent injection of thiopentone while the patient breathes a gradually increasing concentration of trichlorethylene vapour.

2. The injection of a dose of thiopentone sufficient to produce unconsciousness, followed by the inhalation of ethyl chloride or di-vinyl ether. When the depth of anæsthesia has passed into the third stage the inhalation of trichlorethylene is commenced.

3. Induction by the inhalation of either ethyl chloride or di-vinyl ether. When the depth of anæsthesia has reached the third stage, a change is made to trichlorethylene.

4. The inhalation of pure nitrous oxide till loss of consciousness, when oxygen in gradually increasing amount is added together with trichlorethylene vapour. The use of trichlorethylene to supplement nitrous oxide in dental practice is described by G. Kaye (1951).

5. Injection of thiopentone and a relaxing agent with immediate intubation, and inhalation of trichlorethylene vapour with air, or nitrous oxide and oxygen.

The giving of a single small injection of thiopentone followed immediately by the inhalation of trichlorethylene is not usually a satisfactory method of inducing anæsthesia, as the effect of the thiopentone will wear off before the trichlorethylene has taken effect, and there is a period of excitement possibly with coughing and vomiting.

The Problem of Slow Recovery.

The factors concerned in a general way with the length of time taken for recovery from a general anæsthetic will be considered first.

Because of the copious blood supply of the brain, the concentration of an anæsthetic agent in the brain is closely related to the blood concentration of the agent. After an anæsthetic administration the blood concentration of the anæsthetic agent falls, and at a certain point consciousness

returns. Trichlorethylene is mostly excreted unchanged through the lungs, though some is metabolized to trichloracetic acid (Osterlere, 1953).

The rate of excretion of a volatile anæsthetic agent through the lungs depends upon three factors: (*a*) the molecular weight of the agent, (*b*) the boiling point, (*c*) the effective blood concentration. Trichlorethylene has a high molecular weight of 131·5, and for this reason does not easily diffuse across tissue membranes as do anæsthetic agents with low molecular weights. Trichlorethylene boils at 87·4° C., and does not as easily pass into a vapour as agents with lower boiling points. Finally, the effective blood concentration of trichlorethylene is stated to be about six milligrammes per 100 cubic centimetres, so that the pressure gradient upon which the diffusion across the alveolar membrane depends is low. All these factors combine to make the blood concentration of trichlorethylene fall slowly from the effective level. It is to be noted that recovery is rapid from anæsthesia with nitrous oxide, which has a low molecular weight, low boiling point and high effective blood concentration (the reverse of the properties of trichlorethylene).

Recovery from the anæsthetic state depends upon the elimination of all the agents depressing the central nervous system. These include the anæsthetic agent and other depressing drugs given before or during the operation (hypnotics, narcotics, scopolamine, thiopentone and pethidine). In the case of trichlorethylene anæsthesia, any non-volatile central nervous system depressants given combine with the remaining trichlorethylene to maintain unconsciousness. Because these drugs depress respiration and metabolism, they further delay the excretion and metabolism of trichlorethylene.

When trichlorethylene is administered without other depressing drugs, the period of recovery is not unduly long. It is otherwise when the patient is heavily premedicated with hypnotics, narcotics or the newly developed drug "Chlorpromazine".

For these reasons it is suggested that premedication before trichlorethylene should be light—for an adult the administration of "Chloretone", 15 grains, or 50 milligrammes of pethidine, the former by mouth and the latter by injection. It might be observed that the correct mental preparation of the patient for operation is more important than sedative drugs.

Finally it is advised that no more trichlorethylene should be given than is just sufficient to keep the patient in light third stage anæsthesia. If the operation is to be really long (for example, some neurosurgical procedures) it is better to administer trichlorethylene with nitrous oxide and oxygen rather than air, as this will allow a further lowering of the trichlorethylene concentration.

The Problem of Tachypnœa.

The development of tachypnœa during trichlorethylene administration has been explained by Whitteridge and Bühlbring (1946) as due to sensitization of nerve endings in the lungs, with curtailment of inspiration and expiration. The intravenous administration of pethidine was suggested as a treatment for the tachypnœa by Michael Johnstone.

One's own experience suggests that if a patient has a tendency to tachypnœa, administration of trichlorethylene will aggravate it. For example, if a patient is dyspnœic because of secondary malignant disease in the lungs, that patient will almost certainly develop intractable tachypnœa during the administration of trichlorethylene.

Apart from patients who have such a predisposition, others show individual variation; some show tachypnœa almost from the start, and others not at all. The use of pethidine is invaluable; but the writer suggests that it should not be given until the concentration of trichlorethylene is reduced to the least that will maintain anæsthesia. Pethidine should be given intravenously in a small dose. A dose of 25 milligrammes is suggested for an adult. Usually respiration slows and deepens within several minutes of the injection. If tachypnœa returns, the small dose of pethidine may be repeated once, or at the most twice. Should tachypnœa persist and be sufficiently severe, it may be necessary to change to another anæsthetic agent.

Tachycardia and Cardiac Irregularities.

In general, patients who have normal hearts do not show tachycardia or irregularities of heart beat in the absence of tachypnœa. The writer believes that if tachypnœa is avoided or treated, then tachycardia is rarely encountered. On the other hand, patients who already have irregularities of heart beat tolerate trichlorethylene poorly, for it aggravates the irregularity.

Another problem is presented by the injection of adrenaline during trichlorethylene anæsthesia. The injection of solutions of adrenaline during general anæsthesia is a very valuable method of obtaining an operation field free from troublesome oozing. It must be remembered that adrenaline is an extremely potent drug, which is capable of producing dangerous circulatory changes when given in excessive amounts during any general anæsthetic administration, or even in the absence of general anæsthesia. Braun, as a result of experimentation, decided that the best dilution of adrenaline was one in 200,000. The writer believes that this is correct, and that this dilution should be regarded as the standard one. If a small injection is to be made into a vascular area such as a nasal septum, it is thought that a dilution of one in 100,000 is permissible, but that this dilution is the absolute maximum. Incidentally, adrenaline should be carefully measured with a one cubic centimetre syringe, and the amount should not be guessed with the use of an eye dropper. Excessive amounts of adrenaline in excessive concentration are capable of causing arrhythmias during trichlorethylene administration, but it is believed that the injection of the concentrations mentioned above does not produce measurable circulatory changes. When a surgeon asks if he may inject adrenaline during trichlorethylene anæsthesia, the correct answer is: "Yes, if the accepted rules for the use of adrenaline are observed."

The Problem of Chemical Instability.

Despite the addition of a stabilizing agent to trichlorethylene, the tendency to decomposition remains. Langton Hewer (1953) mentions this. It is suggested that the best way of overcoming this is to regard trichlorethylene as expendable, to pour only a small amount into the vaporizer, and to discard it after each session.

Certain Problems of Maintenance.

Trichlorethylene anæsthesia maintained by the insufflation of trichlorethylene vapour through a Davis-Boyle gag is considered by many to be satisfactory for tonsillectomy. One difficulty experienced in cold weather is that of delivering a sufficient concentration to maintain anæsthesia. Most anæsthetists leave their trichlorethylene vaporizers in their motor-car at night, and in the morning they are quite cold. The writer has had a large capacity stainless steel tank made to hold the bottles of his "C.I.G." ether-trichlorethylene vaporizer. In cold weather the bottles are placed in the tank, which has been filled with water at about 80° F. This has been found very satisfactory, and has largely removed the difficulties of this form of anæsthesia.

Conclusions.

The following suggestions regarding the use of trichlorethylene are made:

1. Do not use it for patients who are already dyspnœic.
2. Do not use it when there is irregularity of heart beat.
3. Precede trichlorethylene anæsthesia by a minimal amount of pre-operative medication.
4. Effect the induction of anæsthesia by preceding the inhalation of trichlorethylene with a more quickly acting agent.
5. Use pethidine when necessary to control tachypnœa.
6. Regard trichlorethylene as expendable, and discard it after each session.
7. Warm the vaporizer in cold weather for use with the Davis-Boyle gag.

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HEPATIC CHANGES IN HUMAN BRUCELLOSIS.

By R. A. JOSKE[1] and E. S. FINCKH.[1]

From the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital.

BRUCELLOSIS as a cause of undulating fever is well known. It is perhaps less widely accepted that infection with brucella organisms may produce a variety of clinical patterns, depending on the tissues or organs involved, and it has recently been stated (Barrett and Rickards, 1953) that "it would be no exaggeration to say that brucellosis competes with syphilis in the variety of its clinical manifestations".

Hepatic lesions in brucellosis have been known to occur for many years (Hughes, 1897), but only recently has it been realized that the liver is commonly involved. In the United States of America, Spink *et alii* (1949) studied liver specimens from 11 subjects of brucellosis and found abnormal appearances in all, while in England Barrett and Rickards (1953) performed liver biopsies in 12 cases of chronic brucellosis and found abnormalities in all. Brucellosis must therefore be borne in mind as a cause of clinical liver disease, and for this reason the present paper reports findings in 20 proven cases of brucellosis, 10 of the patients having been subjected to liver biopsy.

Clinical Notes.

The 20 patients comprised 17 males and three females, their ages ranging from nineteen to fifty-eight years, although 13 of the 20 were in the third and fourth decades (Figure I). In only two cases was the infection closely related to occupation, both patients being stock inspectors. Three of the patients were students.

Duration of History.

Fourteen of the cases were considered to be acute, the illness being of less than three months' duration. The remaining six patients, including one female, had longer histories of up to four years' duration. These patients were considered to have entered the chronic stage of the disease.

Clinical Picture.

The clinical pictures presented by these patients were remarkably varied; in only three was a presumptive diagnosis of brucellosis made on admission to hospital. In six cases the initial diagnosis was "pyrexia of unknown origin", and in three tuberculosis was considered probable, whilst two patients had predominantly neurological lesions and one patient presented with polyarthritis.

In five of the 20 cases, the symptomatology was related chiefly to the gastro-intestinal tract. One of these patients had evidence of chronic hepatitis, and two had diarrhœa suggestive of colitis. Two were considered to have viral hepatitis; one of these was jaundiced, and a liver biopsy showed an appearance which was typical of infectious hepatitis of moderate severity. This patient was found, on a subsequent admission to hospital fourteen months later, to have brucellosis, and for this reason only the findings during the second period in hospital have been included in the following analysis.

[1] Working with a grant from the National Health and Medical Research Council.

Symptoms and Signs of Gastro-intestinal Involvement.

The commonest indication of gastro-intestinal involvement was tenderness in the right upper quadrant of the abdomen, noted in seven of the 20 cases. In five the spleen was palpable and in three the liver was enlarged. One

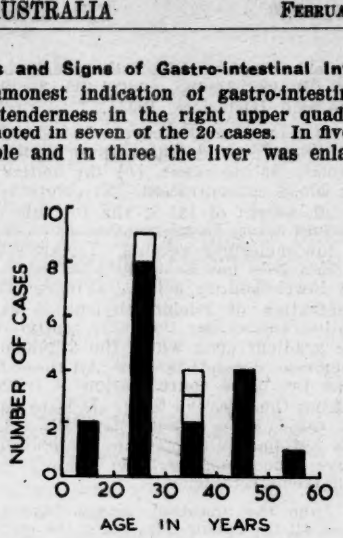


FIGURE I.
Age and sex incidence of 20 cases of brucellosis: open squares, females; closed squares, males.

patient had enlargement of both liver and spleen with ascites and spider nævi. Two patients were jaundiced and two had persistent diarrhœa (figure II).

In eight cases there were no symptoms or signs related specially to the alimentary tract.

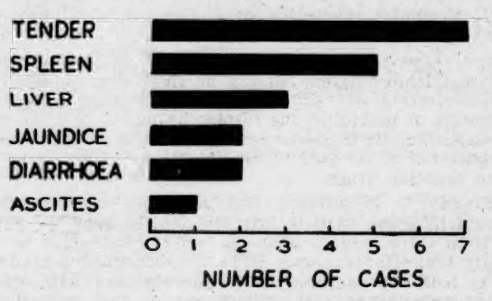


FIGURE II.
Symptoms referable to the alimentary canal in 20 cases of brucellosis. "Tender" = tenderness over the liver; "spleen" = splenomegaly; "liver" = hepatomegally.

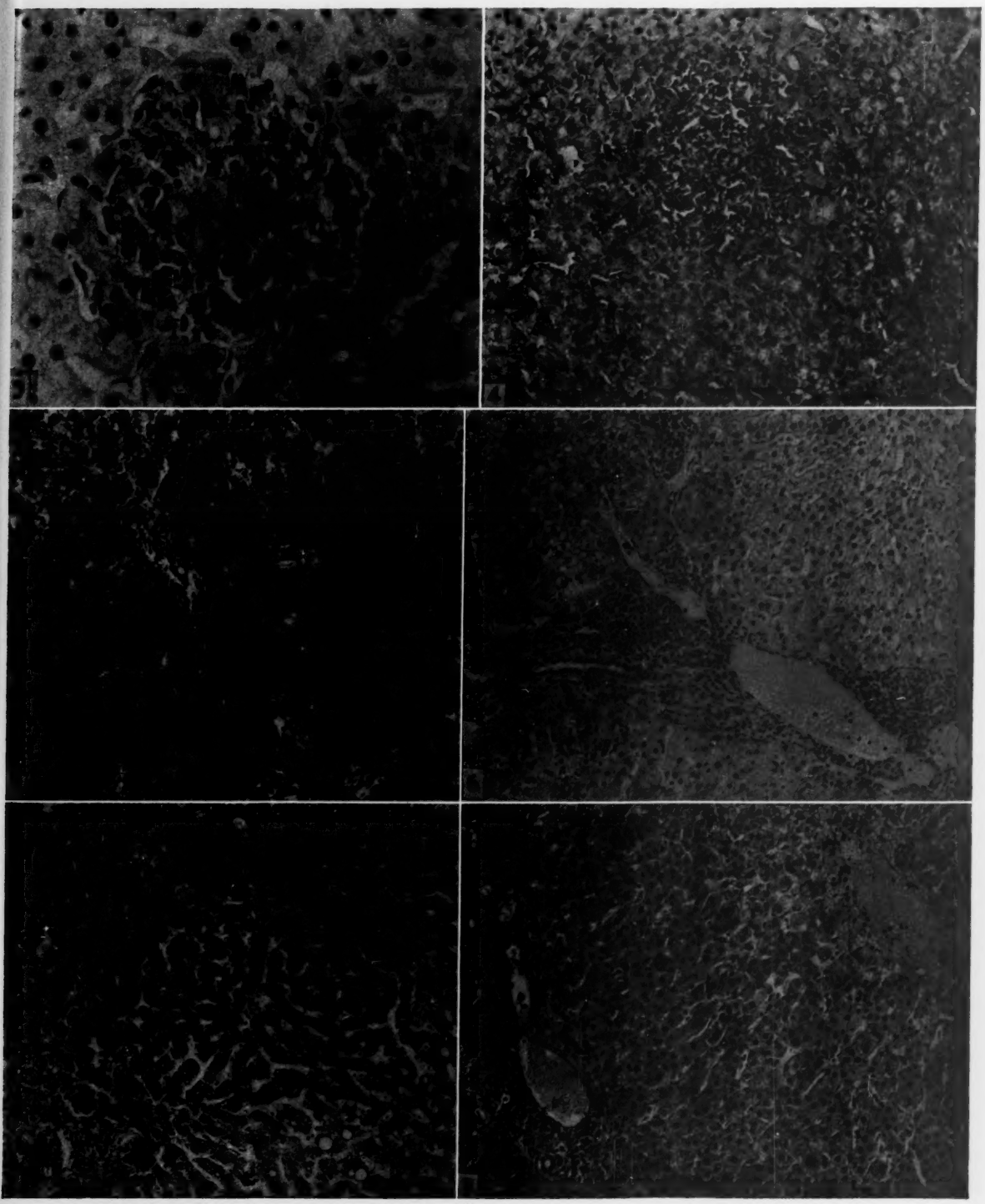
Diagnosis.

All patients had an antibody titre to *Brucella abortus* of 1:320 or higher, and this level was considered to be diagnostic of brucellosis. In two cases the diagnosis was confirmed by isolation of *Br. abortus*, in one instance from the blood, and in the other from the lesions of suppurative parotitis (Joske and French, 1953).

On epidemiological and serological evidence the organism in all cases was thought to be *Br. abortus*. *Br. melitensis* is not endemic in Australia, and *Br. suis* has not yet been isolated from man in this country, although there is some epidemiological evidence that it may have caused some cases of brucellosis in Queensland (Derrick and Brown, 1950). *Br. abortus*, on the other hand, is widespread in cattle throughout Australia (Albiston, 1929; Gregory, 1954).

One patient first developed symptoms after possible inoculation with *Br. abortus* strain 19, which is now known to be capable of causing disease in man (Gilman, 1944; Spink and Thompson, 1953; Editorial, 1954). However, no isolation of the organism was effected in this case.

ILLUSTRATIONS TO THE ARTICLE BY R. A. JOSKE AND E. S. FINCKH.



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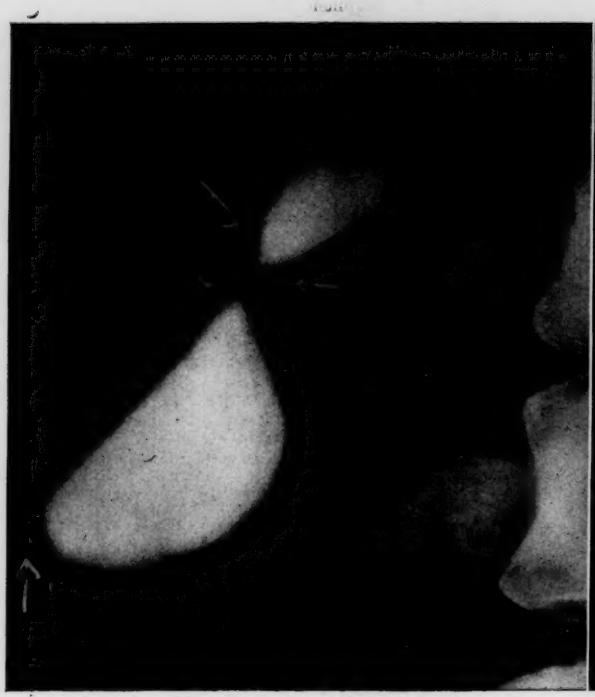


FIGURE I.
Case I, twenty-five minutes after a fatty meal.

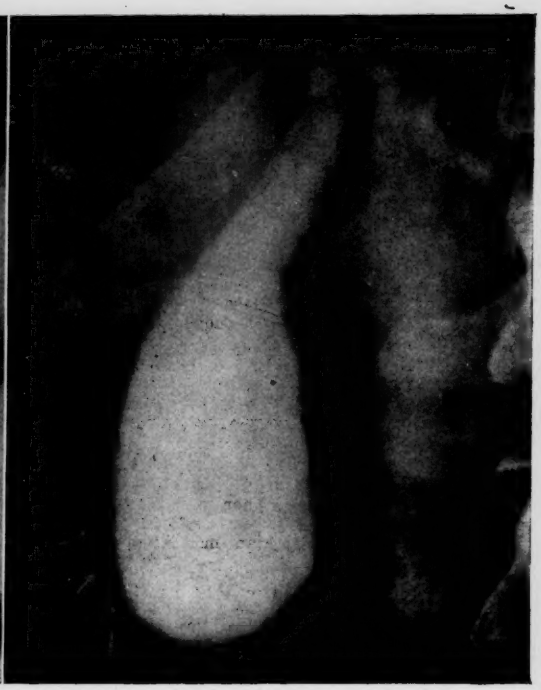


FIGURE II.
Case III, ten minutes after a fatty meal.

ILLUSTRATIONS TO THE ARTICLE BY M. L. POWELL AND H. G. HILLER.

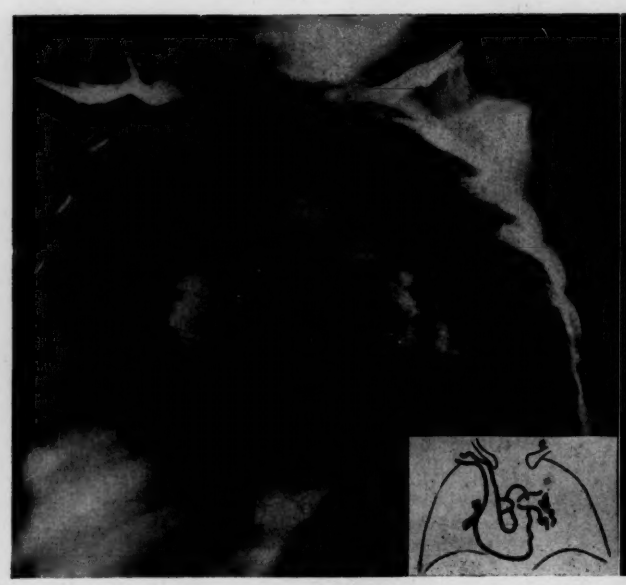


FIGURE I.

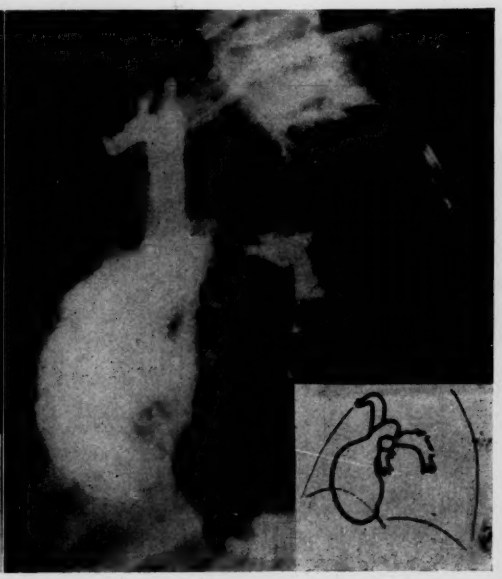
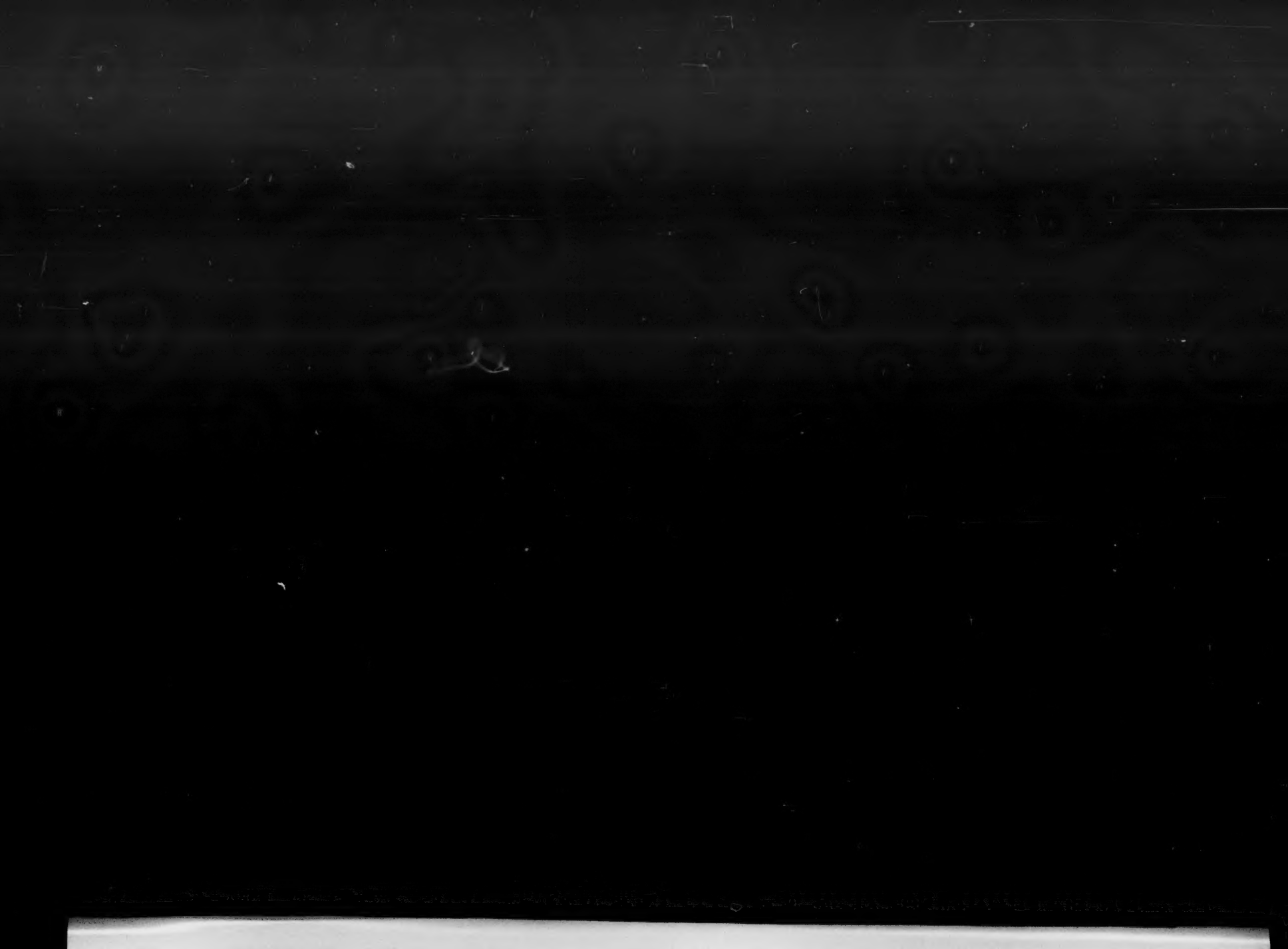


FIGURE II.



Hæmatological Findings.

Two patients had slight anæmia, one leucopenia and three slight leucocytosis.

Liver Function Tests.

Liver function tests were performed in only a proportion of cases. The serum bilirubin level was elevated above one milligramme per 100 millilitres in two of six cases in which it was estimated; both patients had jaundice. In three of six patients the cephalin flocculation test result was positive, and all the patients had chronic brucellosis. Two of them showed gross hæmosiderosis on liver biopsy (*vide infra*).

The serum protein contents were estimated in eight cases, with normal results in seven. One patient with chronic hepatitis had an inverted albumin-globulin ratio and an elevated γ globulin level of 3·5 grammes *per centum*.

The serum alkaline phosphatase content was above 15 King-Armstrong units in three of five cases in which it was estimated, one patient having chronic brucella hepatitis (Table I) and one gross hæmosiderosis. In the remaining case no explanation was apparent.

Pathological Findings.

A total of 13 biopsies was performed on 10 patients, by means of the technique of King and Perry (1949).

Only one of the biopsy specimens showed completely normal appearances, although in three others the changes were only slight. Three of these four specimens were obtained after the patient had received adequate chemotherapy; earlier specimens from one of these patients had shown considerable change. The fourth specimen was from a man aged twenty years, with a two weeks' history of pyrexia, from whose blood *Br. abortus* was isolated, and whose response to therapy was poor.

In five specimens there were well-defined granulomata (Figure III). These were usually composed of epithelioid cells, fibroblasts and lymphocytes, and occasionally contained plasma cells or giant cells. In a few instances they were more poorly outlined and were largely composed of rather more elongated epithelioid cells (Figure IV). Their situation in the lobule varied; some were seen in the liver parenchyma, and were unrelated to portal tracts or central veins, while others adjoined the portal triads (Figure V).

In nine specimens the portal tracts were infiltrated with lymphocytes and fibroblasts, and there was an increase of collagen fibres. The infiltration and fibrosis were slight in five specimens, but in two it was moderately severe and in two it was severe (Figure VI). Where a granuloma adjoined an infiltrated and fibrosed portal tract, it merged with the fibrosis (Figure V), and in one instance the portal tract fibrosis was extensive and composed of rather plump fibroblastic cells, so that the whole area of fibrosis resembled a rather diffuse granuloma (Figure VII).

In addition, the polygonal cells in two specimens contained large numbers of brown granules which stained for iron (Figures V and VII); in both of these the other changes were considerable. In three specimens a few polygonal cells showed fatty change (Figure VII).

One of the 13 biopsies was performed fourteen months before the patient was shown serologically to be suffering from brucellosis. The history, the clinical findings and the results of biochemical liver function tests at this time were typical of acute infectious hepatitis. Histological examination showed centrilobular polygonal cell necrosis, bile staining of polygonal and Kupffer cells and moderately extensive infiltration of the portal tracts with lymphocytes and plasma cells (Figure VIII). These appearances were typical of acute infectious hepatitis, and it was not until a further biopsy was performed on the patient's subsequent admission to hospital fourteen months later that histological evidence of brucellosis in the form of granulomata (Figure III) was found in addition to serological evidence.

In one case autopsy material became available when the patient died. The liver biopsy four years previously had shown a moderate degree of portal tract fibrosis and infiltration, and at autopsy advanced cirrhosis was found. The earlier history of this patient has been published previously (Joske and French, 1953); but the interest of the case is such that the latter part of the clinical history and the autopsy findings are summarized below:

A., a male patient, aged fifty-eight years, was first examined in the Clinical Research Unit on February 21, 1950, when he was admitted with a nine months' history of tiredness, lassitude, cramp in the limbs and fever. On examination, he was icteric, with spider nævi, hepatosplenomegaly and ascites. The clinical diagnosis of chronic hepatitis was confirmed by biochemical tests (Table I) and liver biopsy. His antibody titre to *Br. abortus* was 1: 1280. He was treated conservatively at first, and later received "Aureomycin" and then sulphonamides and streptomycin.

TABLE I.

Laboratory Findings in a Case of Chronic Hepatitis Probably Due to Brucella Abortus.

Date.	Serum Bilirubin Content. (Milligrammes per 100 Millilitres.)	Cephalin Flocculation.	Serum Albumin Content. (Grammes *per Centum*.)	Serum Globulin Content. (Grammes *per Centum*.)	Gamma Globulin Content. (Grammes *per Centum*.)	Serum Alkaline Phosphatase. (King-Armstrong Unit.)	Hæmoglobin Value. (Grammes *per Centum*.)	White Cells per Cubic Millimetre.	Antibody Titre to *Brucella Abortus*.
February, 1950	1·8	++	2·9	5·2	—	16	14·6	3900	1/1280
March, 1950	1·5	+++	3·3	5·0	—	18	—	—	—
July, 1950	1·0	+++	2·0	5·4	2·7	15	13·3	—	1/640
November, 1950	1·0	++	3·4	4·0	2·9	—	13·8	—	1/640
January, 1951	0·5	+++	2·9	4·9	2·9	16	11·9	—	1/640
June, 1951	1·0	++	3·2	3·9	2·4	14	14·4	5300	1/20
October, 1951	—	—	—	—	—	—	—	—	1/320
September, 1952	0·3	+	3·7	2·9	1·9	10	—	—	—
January, 1953	0·3	++	3·4	4·0	2·2	16	15·4	—	1/20,480
April, 1953	1·0	++	3·0	4·4	2·7	25	—	—	1/1280
August, 1953	1·3	++	2·6	3·9	2·7	24	—	—	—
December, 1953	0·3	+++	2·5	4·3	3·1	33	—	—	—
January, 1954	7·5	+++	2·8	4·5	3·5	22	14·2	5000	1/20,480

Early in 1951 he presented with suppurative right parotitis, which responded to surgical drainage and treatment with "Terramycin". *Br. abortus* was isolated from this abscess in pure culture. After this his condition improved only temporarily, and, despite further courses of antibiotics, he still complained of tiredness, anorexia, weakness, muscle pains and insomnia. Liver function tests still showed activity, and his antibody titre to *Br. abortus* was still elevated.

His final admission to hospital was on January 4, 1954, because of persistence of these symptoms. On examination of the patient at this time he was slightly jaundiced and spider nævi were present. The liver and spleen were both enlarged. Œdema was present in the legs and sacral area. He was treated with "Aureomycin" and sulphonamides.

Twelve days after his admission to hospital he developed left pleuritic pain, dyspnœa, cough and hæmoptysis, with increased jaundice. A diagnosis of pulmonary infarction was made and he was given heparin for a few days.

On January 23, 1954, after cessation of heparin therapy, he had a massive hæmatemesis which did not respond to blood transfusion, and he died next day.

At the autopsy, the lower portion of the œsophagus, the stomach and the small and large intestines contained much recent blood clot. This appeared to have come from two small perforations, each two millilitres in diameter, and five centimetres above the cardia, which led into one of a number of large saccular varices in the œsophageal mucosa.

The liver was considerably reduced in size, weighing 1140 grammes. The outer surface was orange-brown in colour and grossly nodular. The nodules measured up to 1·5 centimetres in diameter and alternated with reddish-brown depressions up to five centimetres in diameter. In sections, areas of reddish-brown granulation tissue were seen to alternate with orange-brown liver parenchyma. The gall-bladder was considerably enlarged, and contained two large, dark, facetted stones; the biliary tree was otherwise normal.

The spleen was moderately enlarged, weighing 550 grammes. Its cut surface was firm and elastic.

There was a large wedge-shaped infarct in the lower lobe of the left lung, and the pulmonary artery to this lobe was occluded by an embolus which was surrounded by thrombus. This was adherent to the vessel wall, and the embolus corresponded with the broken-off upper portion of a thrombus in the right femoral vein.

No abnormalities of note were detected in the heart, pancreas, suprarenals, kidneys or brain.

On microscopic examination, post-mortem change made detailed study of the liver difficult. The parenchyma was divided by broad bands of dense fibrous tissue containing proliferated bile ducts, lymphocytes and fibroblasts. The polygonal cells were affected by moderately extensive fatty change, and there was considerable plugging of bile capillaries. In several areas, apparently unrelated to interlobular septa were isolated collections of lymphocytes, fibroblasts and rather plumper cells resembling epithelioid cells; there were no giant cells, and while these areas suggested granulomata it was difficult to be certain owing to loss of cell detail. No appearances suggesting granulomata were seen in other organs.

The patient was considered to have died from massive hæmorrhage from œsophageal varices which resulted from severe cirrhosis of the liver.

Discussion.

The granulomata of brucellosis have been recognized in animal material for many years (Fabyan, 1912), and were first shown in human material by Löffler and von Albertini in 1930, and later by Mettier and Kerr (1934). More recently Sundburg and Spink (1947) found them in bone-marrow biopsies, and Hoffbauer and Spink (1947) demonstrated them in liver biopsies. Other reports have appeared since.

Although characteristic of brucellosis, these granulomata are not diagnostic, for similar lesions may be present in various other diseases such as sarcoid, histoplasmosis, syphilis and *erythema nodosum* (Van Beek and Haex, 1943; Van Buchem, 1946; Klatskin and Yesner, 1950; Finckh *et alii*, 1953). It has been shown (Spink *et alii*, 1949; McCullough and Eisele, 1951) that the granulomata begin as localized areas of hepatic necrosis, situated at random in the liver tissue and due to invasion of the liver cells in these areas by brucella organisms. These areas become infiltrated with polymorphonuclear cells and later by lymphocytes, fibroblasts and epithelioid cells, thereby acquiring the typical appearance of the granuloma.

While the granulomata may adjoin or lie in the portal tracts, a rather less specific infiltration of the portal tracts with lymphocytes, fibroblasts and plasma cells has also been described (Spink *et alii*, 1949). Numerous authors have suggested that this may go on to produce cirrhosis, and McCullough and Eisele (1951) describe fully a case in which the course of a severe necrotizing hepatic brucellosis was followed through to the development of cirrhosis.

In the present series many of these findings have been confirmed, and it is possible that these cases illustrate stages leading towards the development of chronic hepatic brucellosis. In four biopsy specimens small lymphocyte and fibroblast collections were seen in the liver parenchyma. In one specimen (Figure IV) a larger collection of these cells was seen. In five specimens typical fully formed granulomata composed of epithelioid cells and occasional giant cells were noted in the liver lobules (Figure III), while in two specimens granulomata adjoined portal tracts (Figure V). In the latter specimens there was also considerable increase of portal connective tissue, while in nine specimens portal tract infiltration without granulomata was noted (Figure VI). In six specimens there were varying degrees of portal tract fibrosis as well as infiltration, while in one specimen there was slight fibrosis without evidence of inflammation.

Evidence of acute focal necrosis was not seen, but the patient whose earliest liver biopsy specimen presented appearances resembling those of acute infectious hepatitis deserves further comment. In this case there was evidence of polygonal cell loss or damage; this was centrilobular in type and associated with portal tract changes also typical of infectious hepatitis (Figure VIII). Since the clinical similarity between chronic infectious hepatitis and hepatitis in chronic brucellosis has been noted frequently, the possibility of acute brucella hepatitis mimicking acute infectious hepatitis clinically and histologically must be considered. A case in which there was clinical similarity was recently reported by Nusham and Bailey (1953). However, the present case is of little help in this regard, as serological evidence of brucellosis was not obtained until fourteen months later.

It is also possible that virus hepatitis may in some way predispose to or modify hepatic changes in superimposed brucellosis, for both viral hepatitis and brucellosis are relatively common diseases. However, there is at present no information on this point.

In the fatal case reported in this paper the patient died as a consequence of advanced hepatic cirrhosis. The cirrhosis was already established at the time of the first liver biopsy, when serological evidence of brucellosis was also present. Previous infectious hepatitis again cannot be excluded with certainty. However, in this instance *Br. abortus* was isolated from an abscess in the right parotid gland, liver function tests constantly gave positive results, and the patient's general symptoms were of the same type throughout his illness. Furthermore, at autopsy there was some histological suggestion that granulomata of brucella type were present in the liver as well as the extensive non-specific fibrosis.

The relation of the histological appearances seen in the present series to the clinical picture and to therapy is of interest.

All patients with discrete granulomata in their liver biopsy specimens had short histories of less than five weeks' duration; none showed enlargement of liver or spleen, and all had either no therapy, or therapy for only a few days before biopsy. No biopsy specimen from a patient who had received antibiotics in therapeutic doses contained demonstrable granulomata. No other correlations were found between the clinical features and the demonstration of hepatic granulomata. Spink *et alii* (1949) and Barrett and Rickards (1953) have observed granulomata in liver biopsies from subjects of chronic brucella infection, but do not state whether their patients had received antibiotics before biopsy. This suggests that granulomata are seen in

"active" or relatively acute brucellosis, and that they resolve with antibiotic therapy.

Portal tract infiltrations and fibrosis occurred at all stages of the disease, but were more usual in long-standing infection and in patients who responded poorly to therapy.

The two patients with hæmosiderosis of the liver had chronic brucellosis and had received treatment before biopsy. Both had considerable infiltration of the portal tracts, and in both the response to the cephalin flocculation test was positive. Slight fatty change in the hepatic parenchymal cells was seen in three biopsy specimens from three patients. All had chronic disease with enlargement of the liver, greater than would have been expected from the amount of fat seen. Two had received antibiotics before biopsy. This fact may have contributed to the fatty change, since the dietetic history of all patients appeared adequate (Yesner and Kunkel, 1951; Saint and Joske, 1953).

Conclusions.

Two features emerge from this survey—the frequency and the variety of hepatic changes that may be found in human brucellosis. In only one of 13 biopsy specimens were completely normal appearances seen, and the abnormal findings varied from slight lymphocyte collections and discrete granulomata to portal tract infiltration and even established cirrhosis. It is thus apparent that liver biopsy is of value in the diagnosis of brucellosis, and, conversely, that brucella infection must always be considered in the differential diagnosis of obscure liver disease, either acute or chronic.

Summary.

1. The hepatic changes in 20 cases of proven brucellosis at the Clinical Research Unit of the Royal Melbourne Hospital have been reviewed.

2. In 12 cases there were symptoms or signs related to the alimentary tract; these included abdominal tenderness, enlargement of liver or spleen, jaundice and diarrhœa.

3. Abnormal results to liver function tests were not infrequent.

4. Twelve of 13 liver biopsy specimens obtained from 10 patients showed abnormalities, including small lymphocyte collections, specific epithelioid cell granulomata, portal tract infiltration and fibrosis, hæmosiderosis and fatty change.

5. One patient with chronic brucellosis and cirrhosis came to autopsy, having died from massive hæmorrhage from œsophageal varices. It is considered likely that this cirrhosis was a form of chronic brucella hepatitis, and that the other cases studied represented less advanced forms of hepatic brucellosis.

Acknowledgements.

Our thanks are due to the physicians who referred these patients to us, and to Dr. Ian Wood and our colleagues at the Clinical Research Unit for continued help with this study.

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Legends to Illustrations.

FIGURE III.—Liver biopsy from a male patient, aged forty-three years, who presented with pyrexia. Maximum titre 1: 320. He had been in hospital fourteen months previously with acute viral hepatitis (Figure VIII). The biopsy shows a typical granuloma, comprising a central zone of epithelioid cells and an outer zone of lymphocytes and fibroblasts. This granuloma was unrelated to a central vein or a portal tract. (Hæmatoxylin and eosin stain, × 400.)

FIGURE IV.—Liver biopsy from a male patient, aged twenty-one years, who had had intermittent pyrexia for three weeks, and a short pyrexial illness five weeks previously. Maximum titre 1: 2560. The biopsy shows a small, rather diffuse granuloma, in which the central cells resemble elongated epithelioid cells and the outer cells fibroblasts and lymphocytes. This granuloma was not near a central vein or portal tract. (Hæmatoxylin and eosin stain, × 200.)

FIGURE V.—Liver biopsy from a male patient, aged twenty-nine years, who had complained of lassitude for six months and intermittent fever for one month. Maximum titre 1: 640. There are three almost confluent granulomatous areas comprising epithelioid cells, lymphocytes and fibroblasts which adjoin a portal tract. There is a multinucleated giant cell in the centre of the right-hand granuloma, and a small bile duct can be seen in the lower right-hand portion of the figure. Liver cells adjacent to the granulomata contain many dark granules, which stained for iron. (Hæmatoxylin and eosin stain, × 200.)

FIGURE VI.—Liver biopsy from a male patient, aged thirty-nine years. He presented to hospital with pyrexia of six days' duration, and tuberculosis was at first thought to be a possibility. Maximum titre 1: 2560. The figure shows extensive portal and interlobular infiltration with lymphocytes and fibroblasts, but no granulomata. (Hæmatoxylin and eosin stain, × 200.)

FIGURE VII.—Liver biopsy from a male patient, aged thirty-two years, who had had recurrent bouts of pyrexia for four years. Maximum titre 1: 320. There is diffuse granulomatous fibrosis in the left and upper portions of the figures; this fibrosis surrounds a portal tract and extends outwards along interlobular septa. The cells comprise rather plump fibroblastic cells, but cannot be exactly labelled epithelioid. The adjacent liver cells contain many dark granules which stained for iron; a few contain fat. (Best's carmine stain, × 200.)

FIGURE VIII.—Liver biopsy from the same patient as Figure III, taken at the time of his first admission to hospital. The appearances are typical of acute infectious hepatitis. There are necrosis and loss of polygonal cells around the central vein in the right-hand side of the figure. Some adjacent liver cells are multinucleated and regenerating. The portal tract on the left-hand side of the figure is infiltrated with lymphocytes, fibroblasts and plasma cells. (Hæmatoxylin and eosin stain, × 200.)

CHOLECYSTITIS GLANDULARIS PROLIFERANS
(DIVERTICULA OF THE GALL-BLADDER).

By L. IAN BURT AND H. MASEL,
Brisbane.

SINCE Malpighi in 1666 mentioned "small miliary glands" in the gall-bladders of animals which had a branched structure and which he thought secreted bile, numerous authors have shown great interest in structures with a similar appearance in the human gall-bladder, as shown by an extensive historical survey by Robertson and Ferguson in 1945, giving 107 references to the subject. These structures have been variously described as Luschka's crypts, Rokitansky-Aschoff sinuses, diverticula of the gall-bladder, *cholecystitis cystica* (Bodnar) and *cholecystitis glandularis proliferans* (*cystica*). King and MacCallum, of Melbourne, coined the last term in 1931, and this name is now widely quoted in text-books of pathology. There is, however, considerable controversy regarding the ætiology and significance of these diverticula, and up to 1948 their macroscopic and microscopic features had been described only by pathologists. March, in 1948, stated that he was the first to describe their radiological features, and since then sporadic references to them have appeared in radiological literature.

In the practice of one of us three cases showing the above-mentioned structures have been diagnosed radiologically in the last twelve months, and it is thought that they will be seen more often in the future, since the advent of new cholecystographic media, such as "Telepaque", which have a higher iodine content than "Pheniodol" or "Priodax". Two of these cases will now be described in detail.

Reports of Cases.

CASE I.—Mrs. X, aged forty-six years, without children, presented on November 14, 1953, with severe epigastric pain of one month's duration and becoming worse. The patient said that for perhaps ten years she had suffered from attacks of nausea of a mild nature and from headaches; she had also had dysmenorrhœa and recently a very heavy loss at the menstrual periods, but otherwise she enjoyed good health. There was no significant family history. The pain was referred to the mid-epigastrium, and was constant and nagging and associated with some nausea. It was increasing in severity. There was no relation to meals or exercise. There were no symptoms referable to any other system, and no indigestion of any sort.

Examination revealed the patient to be an otherwise healthy woman, who complained of a little epigastric tenderness, insufficient to be significant. While the pain was in the mid-line, the tenderness was more to the right. The dysmenorrhœa and heavy loss at the menstrual periods appeared to be due to fibroid tumours of the uterus.

A cholecystographic examination was carried out. The preliminary film showed no opaque calculus in the gall-bladder region. A film taken thirteen hours after "Telepaque" had been given showed that the gall-bladder had concentrated well; there was narrowing in its upper portion, with irregularity on both aspects of the narrowed portion, more pronounced on its outer aspect; there was also slight irregularity on the outer aspect of the lowest part of the gall-bladder. A series of films taken from twenty-five to fifty-two minutes after the ingestion of a fatty meal showed delayed emptying time; the narrowing and irregularities mentioned above are constantly present on the films.

These appearances are unusual, and they strongly suggest localized chronic cholecystitis with multiple herniations of the mucosa through the muscular layer, the so-called Rokitansky-Aschoff sinuses. The localized inflammation and fibrosis give rise to a "double gall-bladder" appearance and this was also seen in Case II.

At operation there were signs of cholecystitis without a calculus being found; the gall-bladder wall was thickened, especially near the mid-body. There were also signs of recent cholecystitis, which included soft adhesions (filmy) of the omentum *plus* injection of the peritoneal coat. The pancreas, stomach, duodenum and common bile duct all appeared normal. A very careful search was made of all organs to exclude other disease.

On macroscopic examination the gall-bladder was slightly thickened except near the mid-body, where thickening was gross enough to subdivide the lumen into two sections connected by a narrow lumen.

The pathologist (Dr. George Taylor) reported as follows. The gall-bladder was sectioned in three places—the tip, the constricted area and the fundus. The mucosa was thickened and hypertrophied. The subepithelial tissue was œdematous and contained a few inflammatory cells, the muscle was hypertrophied, and there were many cystic hypertrophic glands external to the muscular coat.

The condition was compatible with Rokitansky-Aschoff sinuses of the gall-bladder.

Since operation the patient has been symptom-free—a period of three months. It is thought that her gall-bladder was the cause of the pain, (*a*) because of the absence of other abnormality, and (*b*) because of the immediate and complete relief of pain.

A second case, in which the appearances were very similar to the foregoing, was encountered in February, 1953, but no operative or pathological data are available, as the patient has not been subjected to operation. The patient was a middle-aged female with rather indefinite dyspeptic symptoms.

CASE III.—The third case is particularly interesting, in that it seems likely that it demonstrates a very early stage in the development of these structures. The patient was a female, aged forty-four years. She had suffered from vague pains in the upper part of the abdomen for the past six to eight months, with fullness after meals and flatulence. Two months prior to examination she had an attack of pain extending across the epigastrium, with tenderness from the mid-line extending to the right hypochondrium. The attack lasted for several hours, and she had a similar, though less severe, attack one month prior to examination. She had had a tendency to mild diarrhœa for the last month.

Examination of the patient revealed tenderness in the epigastrium, in the mid-line and slightly to the right. X-ray examinations with a barium meal and a barium enema and chest X-ray examinations gave negative results.

A cholecystographic examination was carried out. Films taken thirteen hours after "Telepaque" had been given showed that the gall-bladder had concentrated well and that it was normal in size and shape.

A series of films taken from ten to fifty minutes after a fatty meal showed the gall-bladder to be emptying at a normal rate; on three of the later films small collections of opaque material were seen on the outer aspect of the fundus (Figure III).

These small collections of opaque material resemble what have been described as the Rokitansky-Aschoff sinuses or *cholecystitis glandularis proliferans*, and are due to herniations of the mucosa through the muscular into the perimuscular layer of the gall-bladder. In most cases they are associated with some inflammation; but no other evidence suggestive of cholecystitis was found by the Graham test in this case. It seems possible that these appearances represent a very early stage of the condition, and it would seem justifiable to have further cholecystograms taken at periodic intervals before this gall-bladder is branded as diseased.

Historical Review.

Following Malpighi (1666), Morgagni in 1769 spoke of calculi in the walls of the gall-bladder "surrounded by a membrane produced from the lining of the gall-bladder and formed in glands which opened by very evident orifices". Meckel in 1816 spoke of breaks in the gall-bladder mucosa, which he compared with diverticula in the bladder and intestinal tract.

Luschka in 1858 described invaginations of epithelium into the walls of the gall-bladder (later called "Luschka's crypts").

Rokitansky in 1861 referred to hernial outpouchings of of the mucosa with very narrow duct openings. Luschka in 1863 described blind remnants of bile ducts seen occasionally in that part of the gall-bladder adjacent to the liver (later called "Luschka's ducts"). Aschoff in 1905 denied the existence of true glands in the gall-bladder, but noted invaginations of the epithelium between the muscle bundles along the paths of the vessels. He con-

sidered that stasis causing increased pressure within the lumen changed small crypts to false diverticula. He thought that gall-stones caused the crypts by increasing the pressure within the gall-bladder, and he also mentioned the role of inflammation in causing epithelial proliferation.

Halpert in 1926 first christened these epithelial invaginations the "Rokitansky-Aschoff sinuses". King and MacCallum in 1931, in an article entitled "Cholecystitis Glandularis Proliferans (Cystica)", stated that "though an etymological hybrid might be considered undesirable, the term is suitable from every point of view except that of the classicist". However, this term is considered unsuitable by authorities who have different views as to the ætiology.

Pathology.

The latest available description is that of King (1952), and this is now summarized briefly. He distinguishes three conditions: (i) *cholecystitis glandularis proliferans*; (ii) hyperplasia of biliary ducts—the "true Luschka ducts"; (iii) mesothelial glands.

1. *Cholecystitis glandularis proliferans* is a downgrowth of epithelium into subjacent tissues with the formation of sinuses. The gross features show considerable variation, as follows. (*a*) Sinuses and cysts without cholecystitis. The vast majority are, however, associated with some degree of old inflammatory change, which may not be recognizable macroscopically. (*b*) Sinuses and crypts with acute cholecystitis. The gall-bladder wall is grossly thickened. Sinuses may be confined to the submucous region or may extend into the muscle or through the muscular coat into the subperitoneal coat. Necrosis of the submucous layer in acute inflammation may spread to the deeper layers by way of the crypts, and thus produce localized gangrene of the wall and bile peritonitis. (*c*) Formation of cysts which always communicate with the lumen by a narrow channel, or of wide-necked spaces properly called diverticula. (*d*) Formation of calculi in the crypts, usually of the mixed type. Calculi are seen more frequently in the crypts (when they are present) than in the cavity of the gall-bladder.

Histological examination shows that the sinuses are often lined by typical gall-bladder epithelium; but there may be a change to an intestinal type or even stratified squamous epithelium. Gastro-duodenal glands, mucous glands, and less commonly pancreatic glands may be found.

2. Luschka's ducts are found most often in the subperitoneal coat on the hepatic aspect of the gall-bladder and never communicate with the lumen. They may be found in young infants or in middle-aged adults. Histologically they closely resemble the intrahepatic bile ducts.

3. Glandular structures in the subperitoneal coat, which are quite localized and do not penetrate deeply into the muscle coat, resemble those observed in other parts of the peritoneum.

Ætiology.

One of us suggests that these structures may be developmental variations and, if so, may be symptomless in the early stages and without superadded inflammation. Although Maximow and Bloom (1952) mention the Rokitansky-Aschoff sinuses, they state that "they probably are indicators of a pathological change in the wall of the organ which permits an evagination of the mucosa through the enlarged meshes of the muscular network".

There are two main views as to ætiology. The first is the view propounded by Aschoff in 1905 and elaborated by Robertson and Ferguson (1945). They state that, as a *muscularis mucosæ* is absent from the gall-bladder, the "mucous membrane lies adjacent to loosely arranged and often widely separated bundles of smooth muscle" and "can easily be pressed into the intervening connective tissue spaces, especially along the paths produced by the channels of the lymph and the blood vessels", by an increase in intracystic pressure. The pressure is affected by muscular contractility and by various factors which may, temporarily at least, obstruct the outflow of bile—for example, neurogenic dysfunctional states, gall-stones and inflammatory obstructions. To support this view they cite the experiments of Higgins and Mann on the gall-bladder of guinea-pigs; they demonstrated that the muscle bundles showed an isolated physiological response to normal stimuli, and small temporary herniations of the mucosa were produced as a result.

Robertson and Ferguson stress the similarity of the Rokitansky-Aschoff sinuses to diverticula of the colon and urinary bladder, all being "invaginations of the mucosa of hollow viscera which are supported by more or less irregularly arranged bundles of smooth muscle in their walls". Therefore they consider that they should be more properly called diverticula of the gall-bladder. It is interesting to speculate whether they are predisposing factors towards cholecystitis; if so, they could be classed as one of the ætiological factors of cholecystitis.

On the other hand, King and MacCallum (1931) describe the process as a "downgrowth of the epithelium into subjacent tissues" with "proliferation *in situ*", the proliferative changes being regarded as "the reaction of the epithelial cells to the chemical stimuli occurring in an inflamed gall-bladder". Again, King (1952) states that there is "downgrowth of the epithelium" and that "it is doubtful whether this phenomenon occurs at any time apart from inflammatory conditions". He does not mention the role of increased intracystic pressure.

Radiological Features.

Descriptions in the available radiological literature are rather confusing. Vastine (1934) described a calculus one centimetre in diameter in a diverticulum arising from the fundus of the gall-bladder; microscopic examination of sections of the excised gall-bladder showed many outpouchings of the mucosa between the muscle bundles with the typical appearance of Rokitansky-Aschoff sinuses. He mentioned the possibility that one of these sinuses was the beginning of the diverticulum. He stated that diverticulum of the gall-bladder was not an uncommon finding at operation or autopsy, but that a pre-operative diagnosis was rarely made.

March (1948) stated that a search of the literature had revealed no record of the demonstration of Rokitansky-Aschoff sinuses during cholecystography; he pointed out the "confusing similarity" of *cholecystitis glandularis proliferans* to Rokitansky-Aschoff sinuses in some cases; he stated that visualization was rare, probably because gall-bladders with Rokitansky-Aschoff sinuses were diseased and concentration of bile was usually considerably impaired. He described a case in a female patient, aged twenty-seven years, with a stricture of the upper part of the gall-bladder which was probably congenital, and a greatly thickened lower sac, which apparently represented chronic cholecystitis, showing Rokitansky-Aschoff sinuses.

Ackerman (1948) described a case which he called "diverticulosis of the gall-bladder" in a middle-aged female; there were numerous diverticula arising from the walls of the gall-bladder which protruded beyond the outline of the viscus. He stated that such diverticula, though often described by pathologists, were rarely demonstrated radiologically, because the small ducts were often occluded by an inflammatory process within the gall-bladder, and because of the presence of small stones within the diverticula.

Bean and Culver (1950) reported a case of Rokitansky-Aschoff sinuses of the gall-bladder; they demonstrated stenosis near the neck of the gall-bladder and chronic cholecystitis with visualization of the sinuses below the stricture. They also referred to the rariety of radiographic visualization of the sinuses as contrasted with their relative frequency in pathological specimens, owing to the usual association with chronic cholecystitis. In their case the sinuses were visible only after a fatty meal; they assumed that a weakening of the contractile elements had occurred, but that sufficient contractile power was preserved to force the opaque material into the sinuses.

Ritvo and Shauffer (1952) add to the confusion by including two sections entitled (i) diverticulum of the gall-bladder and (ii) Rokitansky-Aschoff sinuses, without indicating their close similarity. Under "diverticulum" they include a radiograph with a single projection from the infero-lateral margin of the gall-bladder (a diverticulum formation), and then state that diverticula are hernia-like outpouchings of the mucosa which frequently contain small calculi and vary widely in size, and "they should be considered in the presence of small, irregular or rounded opacities adjacent to the margin of the gall-bladder, particularly when the clinical history indicates disease of the gall-bladder". Under the second heading of Rokitansky-Aschoff sinuses they state that such sinuses are hernia-like outpouchings of the mucosa which extend towards the external layers and do not represent true proliferations of the mucosa; they are characterized in cholecystographic films by a narrow rim of increased density extending concentrically around the peripheral surface of the gall-bladder shadow and separated from it by a thin line of increased radiance. It would have been much simpler if under their heading of diverticulum they had described the solitary type of diverticulum and had discussed multiple diverticula in the same section as the Rokitansky-Aschoff sinuses.

Discussion.

Is it possible to attain order out of the apparent confusion which has resulted from the many different names and descriptions which have been applied to the structures under discussion? Are we dealing with the same disease entity when we talk about *cholecystitis glandularis proliferans*, Rokitansky-Aschoff sinuses, diverticula or diverticulosis of the gall-bladder, Luschka's crypts or chronic *cholecystitis cystica*? We think that they all represent various stages in the evolution of the one disease, whether it starts as herniation or epithelial proliferation or as a developmental variation.

Case III may represent one of the earliest stages of these structures, which is likely to be visible radiologically, and they may have commenced as a herniation resulting from dyskinesia with stasis of bile, or from slight inflammation with epithelial proliferation. It does not seem necessary to postulate inflammation as being always present in the early stages, but it seems likely that inflammation is invariably found in the later stages. Our Case III would be of great interest if the gall-bladder was obtainable for microscopic examination; but in few of these early cases is operation likely to be undertaken. As the pathological condition advances in the gall-bladder, fewer diverticula will be visible on radiological examination, owing to failure of the gall-bladder to concentrate, to blockage of the openings of the ducts by inflammatory œdema, or to the presence of small gall-stones in the diverticula, and these gall-stones will appear to lie in the gall-bladder wall instead of within the lumen. The sinuses could be present perhaps for many years without causing untoward symptoms *per se*, and the patient might later present with the clinical picture of cholecystitis. The fact that sinuses were present would not be recognized if they were not visualized radiologically or if sections of the gall-bladder were not examined.

Even when sections of the excised gall-bladder are examined, the basic condition may be overlooked in the gross inflammation and long-standing fibrosis.

Summary.

1. Three cases are described which would come into the category of diverticula of the gall-bladder or *cholecystitis glandularis proliferans*.

2. Various names, such as diverticula or diverticulosis, *cholecystitis glandularis proliferans* (*cystica*), Rokitansky-Aschoff sinuses, Luschka's crypts and chronic *cholecystitis cystica*, have been used to describe varying degrees of the same pathological condition.

3. A satisfactory solution of this impasse in nomenclature is very difficult, as the term diverticulosis suggests absence of inflammation, while the term *cholecystitis glandularis* immediately stresses the presence of inflammation.

4. While theories as to ætiology differ, it would be better to rely on the two alternative names used in the title of this article.

5. With the advent of higher iodine content cholecystographic media more of these structures should be visualized by cholecystography.

Thanks.

Our grateful thanks are extended to Dr. George Taylor for his pathological report in Case I, to Dr. John Emmett for particulars about Case II, and to Dr. R. Fruchtmann for details about Case III.

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Reports of Cases.

PULMONARY COARCTATION.

By M. L. POWELL, M.R.C.P., F.R.A.C.P.,

AND

H. G. HILLER, M.D., M.R.A.C.P., D.D.R., M.C.R.A.,

Melbourne.

Clinical Record.

DURING 1951 a little boy, aged five years, presented to the Royal Children's Hospital, Melbourne, with a history of tiredness and of failure to gain weight adequately. Exercise produced a moderate degree of dyspnœa. He had been cyanosed at birth, when his mother was told that he had a congenital heart lesion. On examination, he was seen to be a small thin child, with a long, almost continuous murmur at the pulmonary area and some splitting of the pulmonary second sound. No clubbing of the fingers or cyanosis was noted, and the rest of the examination revealed no further abnormality. Investigations, including X-ray films of the chest, fluoroscopic screening, blood examination and an electrocardiogram, were all considered to give findings within normal limits. Angiocardiography demonstrated narrowing of both right and left pulmonary arteries at the bifurcation of the main vessel. Some dilatation of the main pulmonary artery proximal to the narrowing could be seen. (See Figures I and II.) The angiocardiogram was otherwise normal apart from a degree of hypoplasia of the aorta.

Because of the patient's increasing tiredness, cardiac catheterization was carried out recently. This showed a definite fall in pressure across the bifurcation of the pulmonary artery, the pressure in the right pulmonary artery being 15 millimetres of mercury, systolic, and five

millimetres, diastolic, and that in the main pulmonary artery 33 millimetres of mercury, systolic, and five millimetres, diastolic. The right ventricular pressure was difficult to record because of frequent ventricular extrasystoles, but may have been slightly higher than that in the pulmonary artery.

The diagnosis of pulmonary coarctation has therefore been made in this case; but no operative exploration is contemplated at this stage, mainly because the child's symptoms do not appear to warrant it, but also because the right ventricular pressure is not raised to any degree.

Discussion.

As far as is known, only two previous reports of cases of pulmonary coarctation have appeared in the literature.

Schumacker and Lurie (1953), in discussing cases in which pulmonary valvotomy was performed, described one case of this lesion, and in this year Søndergaard (1954) reported three cases. Of these four cases, in three the patients were cyanosed, and showed septal defects and over-riding of the aorta, suggesting Fallot's tetralogy. The fourth case was complicated by an auricular septal defect. The case described in this present article would therefore appear to be the first case of pure pulmonary coarctation reported, and to be the first angiocardiographic demonstration of this lesion.

The condition is a rare one and is not as yet well understood, and no convincing explanation of its cause has so far been forthcoming. Whether it is related to closure of the ductus (as has been suggested with aortic coarctation), or whether some other mechanism is at work, is uncertain.

Acknowledgement.

We should like to thank Dr. Mona Blanch, from whose clinic the child was referred, for permission to publish this case report.

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A CASE OF FIEDLER'S MYOCARDITIS SIMULATING PERICARDIAL EFFUSION.

By ZELMAN FREEMAN, M.R.C.P.,
Sydney.

THIS case is placed on record as an example of a rare but lethal type of heart disease mainly attacking the pre-degenerative age group.

Clinical Record.

The patient was a male boilermaker, aged thirty-six years, who had no relevant previous history of illness which would throw light on his present condition. He had a dubious history of lead poisoning some five years previously; but examination of his urine and stipple cell counts in October, 1951, showed no evidence of this condition. He had not suffered from rheumatic fever, nor was there any immediate antecedent history of a viral infection. His mother had died at the age of forty-seven years from a non-specified heart complaint.

With this background the patient presented on December 20, 1951, with the complaint of moderate dyspnœa on effort, present for four days. It had first become noticeable when he climbed the stairs at his job on the Pyrmont power station. Loss of appetite for the previous two days had been noted, and a soreness (as he described it) in the epigastrium had been present for a similar time. Apart from general malaise and lassitude he had no other symptoms. Interrogation showed that he had temperate habits, his beer intake being one "schooner" per day, and he was not a heavy smoker. He denied having had venereal disease. He had a wife and one healthy child.

Examination revealed him to be a sick-looking muscular male, slightly dyspnœic at rest and appearing faintly icteric. His blood pressure was 110 millimetres of mercury, systolic, and 80 millimetres, diastolic, and gallop rhythm was present at the apex. The left border of the heart was indefinable. Jugular venous engorgement was present with slight œdema at the ankles, and the liver was enlarged four fingers' breadth below the costal margin. His temperature was 99·6° F. and his pulse rate 126 per minute. Examination of the urine revealed a heavy cloud of albumin, but no sugar, and a test for urobilinogen gave negative results. Microscopic examination of his urine revealed a few hyaline casts.

A plain X-ray film of the chest taken on December 21 was reported on as showing the cardiac shadow to be grossly enlarged. The enlargement mainly affected the left ventricle, but there was also some dilatation of the left auricle. A blood count gave the following results: the erythrocytes numbered 4,340,000 per cubic millimetre and the hæmoglobin value was 10·8 grammes *per centum*; the leucocytes numbered 10,000 per cubic millimetre, 61% being neutrophile cells. The blood sedimentation rate was three millimetres in one hour. An immediate electrocardiogram showed an inversion of the *T* wave in lead I with a *QRS* interval of 0·12 second and pronounced clockwise rotation (Figure I).

He was admitted to hospital and put to bed. He was given a salt-free diet, and "Prænitron", "Digoxin", and khellin tablets. The next day the patient said that he felt very well and could lie flat in bed without dyspnœa. However, his blood pressure was only 80 millimetres of mercury, systolic, and 70 millimetres, diastolic, and "Coramine", five millilitres by intramuscular injection, was given twice a day.

The next day (December 24) the patient was still comfortable. Examination revealed *pulsus alternans*, and the liver was still enlarged to about three fingers' breadth below the costal margin.

Two days later the blood pressure was 85 millimetres of mercury, systolic, and 70 millimetres, diastolic, and the "Digoxin" was suspended, because *pulsus bigeminus* was noted; the administration of quinidine, four grains three times a day, was commenced as the nursing staff had noted periods of irregularity of the pulse resembling auricular fibrillation. The patient still felt well and was not heeding his instructions to lie quietly.

On December 29 a further electrocardiogram was taken, and in view of the *QS* patterns in leads V_3R, V_1 and V_2 with inverted *T* waves a provisional diagnosis of antero-septal infarct was made.

On December 30 the patient's condition was noted to be improving subjectively. The next day the blood pressure was 90 millimetres of mercury, systolic, and 80 millimetres, diastolic. On January 3 he again felt slightly better and was playing cards with his visitors on the bed table. However, on January 5 he complained of vomiting with soreness of the abdomen, and this recurred on January 6. His liver was still enlarged, the neck veins were more prominent and the lips were slightly cyanosed. "Digoxin" (0·5 milligramme) was given intravenously, as the vomiting appeared to be due to congestion. The prognosis was becoming obviously more gloomy. On January 7 *pulsus paradoxus* was detected, and it was thought that the patient had all the hall-marks of a large pericardial effusion. That day paracentesis of the pericardial sac was attempted from both the anterior and posterior approaches, without any success. After the injection of one millilitre of mersalyl, it was noticed that practically no urine was passed in response to the injection and the patient had vomited several more times. At this stage he was transferred to Royal Prince Alfred Hospital.

Examination of the patient revealed cyanosis and some orthopnœa, *pulsus paradoxus* was detectable and the jugular venous pressure was considerably raised. His liver was enlarged, firm and tender, and slight œdema of

the ankles was present. The blood pressure was 110 millimetres of mercury, systolic, and 70 millimetres, diastolic. Examination of the urine showed it to contain one-sixth albumin. A blood count taken after his admission to hospital gave the following information: the red cells numbered 5,089,000 per cubic millimetre and the hæmoglobin value was 14·6 grammes *per centum*; the white cells numbered 15,000 per cubic millimetre, 90% being neutrophile cells, 3% lymphocytes and 7% monocytes. The blood urea content at this time was 200 milligrammes per 100 millilitres.

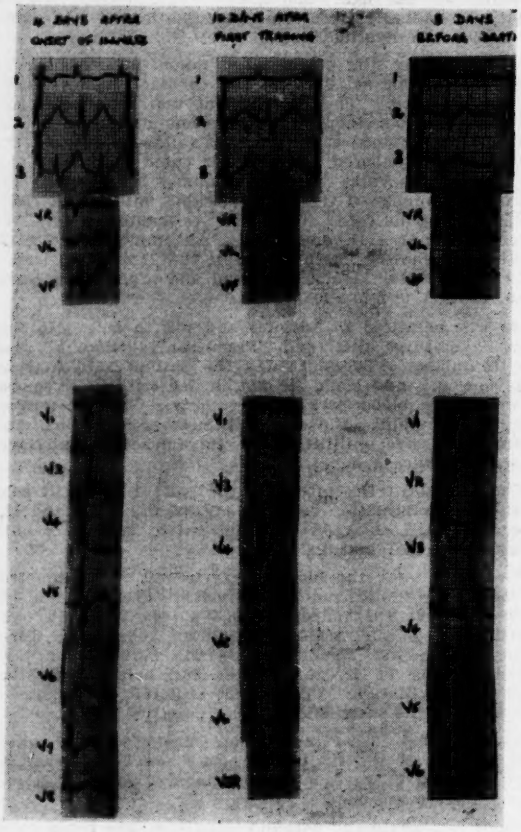

FIGURE I.

Electrocardiogram on left shows notching of *QRS* complex in lead I with inverted *T* wave. The chest leads show upright *T* waves. Middle tracing shows *QS* in V_2R and V_1, with inversion of *T* waves in all the chest leads; a VR shows elevation of *S-T* segment. This suggested antero-septal infarction, but was also consistent with the diagnosis of pericarditis in the "inverted *T* stage".

The patient was radiologically examined in the supine and erect positions; but the result was equivocal with regard to distinguishing an effusion from cardiac dilatation. After repeated attempts at paracentesis of the pericardial sac under fluoroscopic control had failed, cardiac catheterization was performed, and the catheters were visualized radiologically in the right auricle and ventricle and then in the right pulmonary artery. Pressure readings at all these sites were well above normal.

At this stage a diagnosis of non-specific myocarditis was made, and the patient died shortly afterwards.

Comment.

When the problem was reviewed, the diagnosis in the first instance seemed to hinge on the question of whether the epigastric pain was due to an atypical coronary infarction with secondary congestive failure producing the picture. The second electrocardiogram revealed progressive myocardial damage with *QS* patterns in leads V_2R, V_1 and V_2 and inverted T waves. However, if this was taken to suggest infarction, the area involved seemed too small to cause such pronounced clinical findings, and the diagnosis of infarction seemed remote.

The next few days of observation were puzzling, in that the patient lost his dyspnœa, could lie flat on a low pillow with no discomfort and played cards with his visitors. However, after the passage of three weeks during which the venous congestion failed to respond to "Digoxin", a diet of low salt content, quinidine and mercurials, it became necessary to review the diagnosis, as the congestion appeared to be increasing and the signs of cardiac tamponade appeared. These included the abnormal radiological outline of the heart with relatively clear lung fields, the presence of a low blood pressure with a low pulse pressure, gallop rhythm, faint apex beat, obvious jugular venous congestion and *pulsus paradoxus*. This led to an attempted paracentesis, as all the diagnostic signs of a pericardial effusion appeared to be present, although ascites was not prominent as is often the case. The lack of dyspnœa at rest and the lack of radiographic signs of pulmonary congestion in the radiograph all appeared to confirm the diagnosis.

The failure to find fluid and the later evidence of catheterization of the heart proved that the problem was one of cardiac dilatation due to some unknown noxious agent. Beriberi could have been one such agent; but the patient's diet was very good, and a "schooner" of beer a day appeared an inadequate amount of alcohol to cause this. Myxœdema was obviously not the cause, nor was there any suggestion of rheumatic carditis at any time. Murmurs were quite absent, there were no joint symptoms, and the blood sedimentation rate was normal. Recent diphtheria was eliminated by the history and by examination of the fauces. Recent viral or coexistent bacterial disease could not be incriminated. Cardio-vascular syphilis, although not ruled out by a Wassermann test, seemed unlikely as an isolated cause in the absence of a history or physical signs of treponema infection.

Congenital anomalies causing no murmurs appeared very unlikely, and the symptomless past history appeared to exclude this possibility. Familial cardiomegaly and Von Gierke's disease did not seem to fit the diagnosis, as the X-ray appearances suggested dilatation from the start rather than hypertrophy, and the latter usually belongs to a younger age group.

This left two possibilities, sub-endocardial fibrosis and its close relation Fiedler's myocarditis, either of which seemed a likely diagnosis. The latter was first described in 1899; it tends to attack particularly children aged under three years or young adults, and has a uniformly bad prognosis. The course is subacute, lasting only a few months, and the findings are those seen in this patient. Additional symptoms described have been *angina decubitus* in the presence of normal coronary arteries, and additional signs are arrhythmias and bundle branch block. Embolic pulmonary and systemic infarction from mural thrombi occurs, and although this was not observed in the case here presented, ante-mortem thrombi were detected in the trabeculæ of the atria at the autopsy. Two pathological types have been described, one a sterile granulomatous lesion resembling tuberculosis or syphilis and possibly allergic in origin, the other a diffuse lymphocytic infiltration with occasional polymorphonuclear and eosinophile cells and areas of muscle necrosis and œdema. It was to this latter group that the case under review belonged.

The post-mortem examination showed several ounces of blood-stained fluid in the pericardial sac. The heart weighed 375 grammes (normal, about 310 grammes) and was greatly dilated. The tricuspid ring admitted eight fingers, the mitral ring six fingers. There was no valvular abnormality and the *foramen ovale* was closed. Ante-mortem clot was present between the trabeculæ of the atria. The myocardium was uniformly flabby. The

coronary arteries and aorta were normal. The kidneys were enlarged and congested, otherwise normal.

Microscopic examination of the heart revealed slight patchy œdema, considerable thinning of muscle fibres and occasional small collections of lymphocytes. In the atria there was slightly more lymphocytic infiltration, but in no place was this very pronounced or extensive. The muscle in this region was thin and slightly degenerative.

Discussion and Summary.

This case shows that the classical signs of pericardial effusion can be simulated by gross dilatation of the heart with equal damage to both sides, even the highly valued sign of *pulsus paradoxus* being quite pronounced in this case. Other diagnostic pointers described to differentiate the two conditions are the prolongation of the *Q-T* interval in cardiac dilatation and its tendency to shortening in paricardial effusion. In the X-ray film a sharp cardio-hepatic angle is said to be of diagnostic value in favour of effusion rather than dilatation, and William Evans's "stencil" cardiac outline in the radiograph also is said to favour effusion. Likewise a straight left border suggests a collection of fluid.

Radiographs were taken with the patient in the erect and supine positions, but these, although suggesting cardiac dilatation, were not diagnostic.

The *Q-T* interval in this case was prolonged to 0·32 second (normal, up to 0·30 second), the cardio-hepatic angle was not particularly acute, there was no stencilling effect of the cardiac outline, and the left cardiac border was not particularly straight. These pointers were not evaluated at the time, but it is doubtful how much reliance can be placed upon them.

The only accurate method of solving the problem is cardiac catherization, which in the case of cardiac dilatation clearly shows the catheter in the right auricle against the extreme outline of the heart.

To sum up: a male patient, aged thirty-six years, was observed over a period of three weeks gradually deteriorating with a progressive myocardial lesion of unknown ætiology, with a minimal amount of subjective complaint despite a maximal amount of venous congestion; at the post-mortem examination the appearances were suggestive of Fiedler's myocarditis.

Acknowledgements.

I should like to acknowledge assistance received from Dr. John Halliday and the Superintendent of Royal Prince Alfred Hospital.

Reviews.

Woman: Man's Equal? By Adolphe Abrahams, O.B.E., M.D., F.R.C.P.; 1954. London: Christopher Johnson. 7½" × 5", pp. 176. Price: 10s. 6d.

ANY man who sets out to determine whether woman is or is not man's equal will commonly be called brave. At first sight Sir Adolphe Abrahams will be so described, but he does not give a definite answer to his question. No man could. Most men, if they are honest, will realize that some women are more than equal to them and they will surely know women to whom they are superior. The same may be said of most women. The truth, of course, is that man and woman are complementary to one another, though there are some spheres, in which owing to body build, mental or other endowment, either man or woman predominates. Sir Adolphe Abrahams is a medical man of wide experience, and to aid him in the discussion of his subject is the fact that he has acted as Honorary Medical Adviser to the British Olympic Athletic Team. He discusses many human activities in turn and makes a comparative estimate of the characteristics and performances of men and women in them. It is all very interesting, but one wonders whether the effort is really worth while. The historical side of the book holds the attention. The man and woman of today will regard as pathetic Queen Victoria's plea in 1870 to all women of good will "to join in checking this mad wicked folly of 'Women's Rights' with all its attendant horrors on which my poor feeble sex is bent, forgetting every sense of womanly feeling and propriety". The author thinks that the influence of Dickens and Thackeray is largely responsible for an erroneous conception of Victorian woman. "She was probably much as the women of to-day, merely differing from them in the degree of freedom and intimacy of association with men which convention has made possible." The chapter on woman as delinquent and criminal is full of interest and confirms the commonly held view that woman by and large does not do things by halves. She is very like the girl who had a little curl right in the middle of her forehead; when she is good, she is very very good, but when she is bad, she's simply horrid. Other chapters deal with "Marriage, Kinsey and Divorce", "Education, Co-education and Sex Education", "Dress", "Exercise and Athletics" and so on. Readers will find this book attractive; they may gain some profit from its perusal. It could certainly be used as the basis for many an argument.

An Introduction to Physical Methods of Treatment in Psychiatry. By William Sargant, M.A., M.B. (Cantab.), F.R.C.P., and Eliot Slater, M.A., M.D. (Cantab.), F.R.C.P., with a chapter on treatment of the epilepsies by Denis Hill, M.B. (London), F.R.C.P.; Third Edition; 1954. Edinburgh and London: E. and S. Livingstone, Limited. 9" × 6", pp. 370, with four illustrations. Price: 20s.

THE third edition of this book will be welcomed for the authors' evaluations of established techniques and review of new methods and drugs. It cannot be too strongly emphasized that sound diagnosis is a necessary preliminary to treatment, much of which in psychiatry continues to be empirical and lacks a scientific basis. A "rough-and-ready machine of treatment" is to be avoided at all costs, but selection is often difficult, especially in the psychoneuroses, and when one or other form of treatment has failed to produce the results anticipated, something else should be tried. The authors firmly believe in keeping on trying.

Acetylcholine given intravenously in doses up to 0·6 gramme has been reported by Fiamberti to be of value in early schizophrenia. As many as a hundred injections may be needed. Sargant and his assistants are more impressed by their results with smaller doses in certain tension states especially for patients with localized obsessions and phobias. In some 16,000 attendances at an out-patient department 3600 were for acetylcholine, compared with 800 for electro-convulsive treatment.

There has, of course, been much additional experience with leucotomies since the 1948 edition appeared, and not unnaturally the trend is towards earlier intervention in schizophrenics, some 30% of whom may be restored to life outside an institution after failure with other physical methods. Modified and anterior "cuts" benefit patients with pronounced emotional tension, and the authors' series include a number of asthmatic, eczematous and hypertensive subjects.

In the chapter on treatment of the epilepsies, by Denis Hill, the author states that where clinical observation and the electroencephalogram point to a focus of onset in the temporal lobe, the best results are obtained from surgery when the excitable focus has been identified by electro-corticography of the cortex exposed at operation. Emotional, physiological and biochemical factors are reviewed. "Mysoline", "Malidone" and "Milantin" are described as "still on trial".

This new edition will certainly maintain the reputation gained by its predecessors.

The London School of Hygiene and Tropical Medicine. The School and the Site: A Historical Memoir to Celebrate the Twenty-Fifth Anniversary of the School. By Catherine M. Clark, M.A., and James M. Mackintosh, M.D.; 1954. London: H. K. Lewis and Company, Limited. 10" × 7½", pp. 116, with 44 illustrations. Price: 21s.

THIS book is in two parts. In the first part Catherine Clark discusses the history of the Keppel Street site and surroundings, from the time of Henry III. Though she tells an interesting story, most of it has little relation to the London School of Hygiene and Tropical Medicine, which is now the only building in Keppel Street. That the ground on which the school now stands was from the seventeenth century until near the end of the nineteenth century the scene of "robbery and murder and every species of depravity and wickedness of which the heart can think" will not, one hopes, influence the quality of the work now done there. The social classes and the pattern of life in Keppel Street are discussed.

The site was purchased by the Shakespeare Memorial Theatre committee, but lack of funds and the first World War prevented the building of a theatre. The school and the site were a gift of the Rockefeller Foundation, and the building was first occupied in 1929. Professor Mackintosh confines his story to an account of the negotiations for the establishment of such a school and its growth as an institution. It fulfilled an urgent need for coordinated study of public health both by students and research workers. However, until recently funds for general research have been inadequate, most research projects being designated in advance. Patrick Manson's School of Tropical Medicine and the Ross Institute have been incorporated in the new school, and it has grown rapidly in its first twenty-five years. The primary purpose of the London School of Hygiene and Tropical Medicine is the advancement of science in the field of preventive medicine; this book gives the reader no idea of how well it has fulfilled this purpose, for essentially it is an account of a piece of land and a building and will probably appeal to few who are not associated with the school.

Textbook of Pediatrics. Edited by Waldo E. Nelson, M.D.; Sixth Edition; 1954. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 10½" × 7½", pp. 1600, with 438 illustrations. Price: £7 2s. 6d.

THE Griffith, Griffith-Mitchell and Mitchell-Nelson series of "Textbooks of Pediatrics" are extremely well known and are greatly appreciated in pædiatric circles. Professor Nelson has become the sole editor with the collaboration of seventy contributors of high standing in medical schools of the United States of America. The appearance of eighteen new titles in the list of contributions, the condensation in pages from 1658 in the fifth edition, appropriate changes in the copious collections of references and the inclusion of new information which has become available in the past four years are all evidences of the thorough revision which has made this sixth edition appear so soon. This famous text-book is so widely used that the appearance of a new edition is awaited with great interest; new work mentioned in it receives the hall-mark of acceptance.

Among the general factors in the care of sick children we have noticed a change in authorship of the articles on parenteral administration of fluids and certain technical procedures for which Dr. Victor C. Vaughan III has become responsible, and on drug therapy which is now over the name of Dr. William P. Barba II. The excellent section on neonatal care has been taken over by Dr. Clement A. Smith and the anomalies and diseases of newborn infants are now described by Professor Nelson and Dr. Harry H. Gordon.

A short article by Dr. James B. Arey on cytomegalic inclusion disease, usually of infancy, is a novelty which may prove of use in the differential diagnosis of generalized states of blood dyscrasia and hepatic damage. The newly described condition could also be of interest to those who are studying viral damage to the developing fœtus. Other changes in authorship in the section descriptive of infectious diseases have occurred in the articles on protozoan diseases. Dr. A. J. Walker is now responsible for the important account of malaria. Dr. Paul C. Beaver and Dr. Harry A. Feldman share the work on intestinal protozoa.

Professor Julius B. Richmond has joined the distinguished group whose large section on the digestive system has been maintained as authoritative by the consolidation of much new material. Similarly Dr. Samuel Kaplan has reinforced the group at work on the equally important section on the cardio-vascular system. When we come to the articles on diseases of the blood, the spleen, and the lymphatic system, we find that Dr. Louis K. Diamond has gained the assistance of Dr. Nathan J. Smith and Dr. Victor C. Vaughan III. Changes have also taken place in the section on the genito-urinary system from which the opening article on renal anatomy has gone and Dr. Philip L. Calcagno is named instead of Dr. Norton Nelson as the author of the one on physiology. Professor Sherman Little has taken over that portion of Professor Mitchell I. Rubin's large assignment which deals specifically with the disorders of urinary secretion. In Professor Josef Warkany's well-known section on endocrinology we notice the additional name of Dr. Angelo M. DiGeorge, though Professor Warkany is the sole contributor still on skeletal defects. A change in the section on the bones and joints is an additional article by Dr. Lytt I. Gardner on metabolic bone disorders simulating rickets.

In the fifth edition, acrodynia, amyloidosis, glycogen disease, lipodystrophy and lipæmia were grouped together as miscellaneous diseases. In the new edition, acrodynia and amyloidosis together with sarcoidosis appear in a section on unclassified diseases. Glycogen disease has become classified under defective disaccharide metabolism. Lipodystrophy appears as a disturbance in the subcutaneous fat; and lipæmia is separately described in varieties, familial, non-familial and that due to insulin. New sections have been included on neoplasms and other tumours by Dr. James B. Arey, and on γ radiation injury by Dr. Robert W. Miller.

It is clear that libraries and individuals would be wise to obtain the new edition even if the earlier ones are available.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"The Management of Mental Deficiency in Children", by I. Newton Kugelmass, B.S., M.A., M.D., Ph.D., Sc.D.; 1954. New York: Grune and Stratton. 9" × 6½", pp. 324, with 68 illustrations. Price: $6.75.

The purpose of the book is "to reveal the mechanism and management of mental deficiency in infants and children".

"Leg Ulcers: Their Causes and Treatment", by S. T. Anning, T.D., M.A., M.D. (Cantab.), M.R.C.P.; 1954. London: J. and A. Churchill, Limited. 9" × 6", pp. 186, with 42 illustrations. Price: 18s.

An attempt to review the literature and to integrate the knowledge that has been acquired.

"Atlas of Congenital Cardiac Disease", by Maude E. Abbott, B.A., M.D., F.R.C.P. (Canada); 1954. New York: The American Heart Association. 14" × 10½", pp. 72, with 25 plates. Price: $5.00.

An exact reprint of the original monograph which appeared in 1936.

"Review of Medical Microbiology", by Ernest Jawetz, Ph.D., M.D., Joseph L. Melnick, Ph.D., and Edward A. Adelberg, Ph.D.; 1954. Los Altos, California: Lange Medical Publications. 10" × 7", pp. 366, with 92 illustrations. Price: $4.50.

The object has been to make available a brief, accurate, up-to-date presentation of those aspects of medical microbiology which are of particular significance in the fields of clinical infections and chemotherapy.

"Canadian Medical Directory", edited by W. R. Feasby, M.D.; First Edition; 1955. Toronto: Current Publications, Limited. 9" × 6½", pp. 384. Price: $7.00.

The first volume of its kind to be published in Canada.

"The Surgical Clinics of North America"; 1954. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. Pacific Coast Surgical Association Number. 9" × 6", pp. 302, with 35 illustrations. Price: £7 5s. *per annum* in cloth binding and £6 *per annum* in paper binding.

A symposium on the total care of the surgical patient. There are 24 articles with a foreword. Some articles have more than one author.

"The Cerebrospinal Fluid", by S. Lups, M.D., and A. M. F. H. Haan, M.D., with an introduction by Pearce Bailey, M.D.; 1954. Amsterdam: Elsevier Publishing Company, Limited. London: Cleaver-Hume Press, Limited. 9" × 6½", pp. 366, with 93 text figures. Price: 52s. 6d.

The attention is focused on the practical aspect of the subject—for the neurologist, psychiatrist, internist and so on.

"A Synopsis of Medicine", by Henry Letheby Tidy, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (London); Tenth Edition; 1954. Bristol: John Wright and Sons, Limited. 7½" × 5", pp. 1272. Price: 35s.

First published in 1920 when it was devised as a companion to text-books, not a substitute for them.

"Handbook for Medical Officers of Schools on School Health and Communicable Diseases", issued by The Medical Officers of Schools Association; Twelfth Edition; 1954. London: J. and A. Churchill, Limited. 8¼" × 5½", pp. 78. Price: 6s.

The first edition was published in 1885.

The Medical Journal of Australia

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References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

A PÆDIATRIC STUDY OF 1000 FAMILIES IN NEWCASTLE-UPON-TYNE.

IT was one of the contentions of the late Sir James Spence, of pædiatric fame, that the study of pædiatric illness could best be undertaken in the homes of children. In association with Dr. W. S. Walton, Dr. F. J. W. Miller and Dr. S. D. M. Court, who come from the Department of Child Health, King's College, University of Durham, and the Public Health Department of Newcastle-upon-Tyne, he began a study before the second World War. This was interrupted by the war and was resumed in 1947 after the war was over. Shortly before his death, James Spence invited the Nuffield Foundation and the Nuffield Provincial Hospitals Trust to publish the report of the work, and this has now appeared under the title of "A Thousand Families in Newcastle-upon-Tyne: An Approach to the Study of Health and Illness in Children".[1] Before the preface of this book there appears a short statement about Spence, and his fellow authors write that in conception and conduct the survey expresses much of what Spence was and stood for, of the qualities that made him great and at the same time endeared him to young and old both overseas and at home. In reference to the work Spence stated: "In all that followed we tried to remain sensitive to the privilege of access to the homes of our families." This, we are reminded, leads us to the heart of Spence's habits of thinking and living. The book is to be regarded, we read, as a memorial to Spence, a memorial largely of his own fashioning.

We would observe at the outset that the book represents a pædiatric study of the first importance and that no student of pædiatrics can afford to be without it. By the end of June, 1947, the investigators had enlisted 1142 infants from 1132 families. One year later they still had the active cooperation of the parents of 967 children, having lost in the four months 44 children who died, 127 who moved from the city, and only four because the families did not wish to cooperate. This account of infancy in Newcastle-upon-Tyne covers the year May, 1947, to April, 1948. The investigators had their previous experience and preliminary trials to guide them. They express the view that the technique used could not easily be transferred to other communities. They think that their facts about the incidence, the epidemiology and the natural history of disease are more exact than those obtained by the usual methods of gathering vital statistics. The investigators had in turn, as full-time members of the team, Dr. Ruth Cammock, Dr. Hugh Jackson and Dr. George Knox, who made family visits and assisted in the arrangement of the report. The emphasis in the report is on the sick infant in the family, but the authors also describe the environment in which he lived, and they include housing, mental capacity, family structure, social status and health services. They have recorded family finance, but have not described it because they have not been satisfied with the adequacy and accuracy of their facts. The most relevant economic fact was that the survey was carried out at a time of "full employment" when only fourteen fathers did no work throughout the year. Reasons are given for the absence of an exact correlation between housing conditions and the incidence of disease, but nevertheless it is pointed out that the incidence of the severe infections, especially bronchitis, pneumonia and gastro-enteritis, increased as the standards of living and social status declined.

Some interesting facts on environment are given. Judged by statutory definitions, nearly one house in seven was considered unfit for habitation; four houses out of ten lacked a fixed bath; more than one house in four had only an outside water closet shared by two to seven families. Judged by the personal unit standard which the authors describe and define, nearly one family in three was living in overcrowded conditions. Some diseases, such as bronchitis, pneumonia, whooping-cough and recurrent staphylococcal infection, and domestic accidents, were more prevalent in the overcrowded families. Many examples were seen of parents dealing competently and providing adequate safeguards for their children in spite of the dangers mentioned, though this was accomplished only by an exercise of great parental devotion and a high degree of domestic skill. It is important to note that maternal capacity emerged as the chief single factor in the welfare of infants. Maternal capacity was regarded as "satisfactory" in 80%, as "unsatisfactory" in 9%, and as "indifferent" in the borderline cases in 5%. There remained 3% unclassified and 3% in which, owing to definite changes in social or economic circumstances, such as the death of a father or illness of the mother, the quality of the care changed during the year. Within the 9% of unsatisfactory families, there were 20 problem families, 2% of all the families. These problem families represented the lowest order of family life and their failure was due to a grave defect in character or intelligence or to a combination of these defects in both parents. The average number of children within the problem families was 4·3, compared with 2·3 for the remainder of the group. For detailed

[1] "A Thousand Families in Newcastle upon Tyne: An Approach to the Study of Health and Illness in Children", by James Spence, W. S. Walton, F. J. W. Miller and S. D. M. Court; 1954. London: Oxford University Press. Melbourne: Oxford University Press. Published for the Nuffield Foundation and the Nuffield Provincial Hospital Trust by Geoffrey Cumberlege. 8½" × 6", pp. 232, with 15 illustrations. Price: 19s. 9d.

comparisons, 20 is regarded as too small a number, but it is pointed out that the infants in these families had one and a half times the expected incidence of illness and twice the incidence of bronchitis and pneumonia. The basic defects of personality in most of the parents in these cases made wholesome family life impossible, and in the care of their children supervision and support were required. The authors apply this experience to the total population of the city of Newcastle, and they estimate that there are some 1350 children under fifteen years of age living in 300 problem families. This is an incidence of one problem family per thousand of the population. The treatment of problem families is regarded as outside the scope of the report, but it is stated that the remedy will be preventive or palliative—complete curative treatment may be impossible. It is thought that if the scientific method fails to supply an answer or to provide a remedy, it will be best to rely on sentiments of charity and love.

In regard to infantile mortality (deaths per thousand live births within a year of birth), this has fallen remarkably during the past twenty years, but it remains relatively high in industrial towns. In the Newcastle group there were 24 infant deaths in the sample during the first year of life, and this corresponds closely with the prevailing infantile mortality rate of 44 in Newcastle at that time; the contemporary national rate was 41 per thousand. In the study of each individual death, the part played by multiple causes became more and more evident, and to attribute the cause of death to one agent may oversimplify and obscure the real nature of the problem. After elimination of those deaths which were considered to be avoidable, the view is expressed that even under prevailing conditions an infantile mortality rate of less than 23 per thousand should be attainable in Newcastle by the application of reasonable care and medical attention and with the aid of specially designed hospital treatment where and when it is necessary.

The total frequency of illness is stated as follows. Only 203 of the 967 infants had had during the first year of life no recorded illness requiring medical care. The remaining 764 infants experienced 1625 illnesses, some being ill on several occasions; 86% of these illnesses were infective in origin. Respiratory disease was the most frequent cause of death and illness. In various forms it accounted for 57% of 1393 infective illnesses; one infant in five had one or other of the types of bronchitis described; one in ten had whooping-cough; one in fourteen had otorrhœa, and one in twenty had pneumonia. Four kinds of bronchitis are described: acute bronchitis, coryzal bronchitis, wheezy bronchitis, and relapsing bronchitis; to these are added a group covered by the term miscellaneous bronchitis. The assumption is made that these diseases are clinical expressions of a wide range of ætiological agents. A total of 15 infants were found to be infected with tuberculosis; 11 of them had been in intimate or repeated contact with an adult source of infection. In all, at least 62 children had been in contact with adults suffering from tuberculosis. It is important to note that a study of the attitude of parents towards the danger of infection with tuberculosis revealed that, where there was a potential infector in the family, two-thirds of the parents were either not aware of the risk or not concerned to safeguard their infants from it. It is interesting to note that all social groups were represented by the 15 infected children. The fathers included a schoolmaster, a master baker, a clergyman, a clerk, a lorry driver and a coalhewer. None of the families were living in overcrowded conditions and only in three families were the houses structurally defective. All except two children came from stable, happy families. The sage remark is made that these facts have to be remembered when so much stress is laid upon housing conditions as one of the dominant factors in the spread of tuberculosis. There was no evidence that the children who became infected lived under environmental circumstances which were any worse than those of the group as a whole. The symptoms of diarrhœa and vomiting affected about one-sixth of the children in the first year; only in a third of these attacks was the illness associated with significant constitutional upsets. Although the problem of diarrhœa and vomiting is not so urgent as that of respiratory disease, it is still real, and these conditions are among the chief causes of admission of children to hospital in the first year of life. The solution of the problem is made more difficult because severe prolonged attacks of diarrhœa and vomiting are often associated with indifferent medical care or poor maternal observation. We read that the most suitable hospital treatment is found in a medium-sized town if all pædiatric workers are concentrated in one hospital.

In regard to medical care it is pointed out that in their first year of life four out of five children had significant illnesses requiring medical attention. Responsibility for the provision of this fell primarily on the family doctor. His help was first sought in 905 of the 1153 illnesses medically treated, and in 783 he dealt with the matter himself and alone. On 30 occasions the practitioner asked for admission of the child to hospital, and in a further 92 instances he enlisted help and advice in an out-patient consultation at hospital. It is pointed out that the difficulties and uncertainty about the nature and type of illness of infancy demand from the family doctor a high level of diagnostic skill and therapeutic experience for which he requires special undergraduate and post-graduate training; without this the quality of medical care will be inadequate. There is a considerable amount of sickness, some of it serious, for which the parents do not call a doctor. The experience and sagacity of the parents in deciding when a doctor should be called is therefore an important element in the care of sick children. This is, of course, true of any community.

An important chapter is devoted to conclusions and suggestions. At the risk of lengthening this discussion, the following "pertinent facts" which arise must be mentioned. (i) The remarkable decline in disease and deaths in infancy during the last forty years is due primarily to an increase and spread of the knowledge about the proper care and feeding of infants and to a decrease in poverty. (ii) The chief agents of these improvements have been (*a*) those mothers and grandmothers who have sought this new knowledge about the care and feeding of children and applied it to their families; (*b*) the child welfare centres, the health visitors, the newspapers, the radio and other organs of publicity which have spread knowledge in different ways; and (*c*) the public authorities and others who have built new houses. (iii) While the family doctors and hospitals have played an essential part in the diag-

nosis and treatment of established disease, their work has not been responsible for the improvement of child health in the past forty years, mainly for the reason that medical education did not, in that period, equip medical practitioners for a role of preventive medicine. (iv) The universities have contributed to the improvement of child health only in so far as some members of their staffs by researches have advanced and clarified knowledge of nutrition and diseases in childhood. (v) In spite of the improvements in child health during the past forty years, there still remains a considerable volume of disease in infancy which is preventible and beyond that a further volume of disease which, although not preventible, is curable. This will make demands upon research workers for its clear understanding and on trained medical practitioners for its effective management. (vi) There is a limit to the results which the traditional agents of housing, health education and sanitary reform can achieve in the further prevention of disease in childhood. Further prevention will depend mainly on the education of family doctors in the principles of health and development of children and in the prevention of their diseases, and afterwards in the application of their knowledge in their family practices. (vii) An extension of the concepts of family doctoring will depend on a greater knowledge of disease in infancy.

One of the suggestions made deals with medical education. Medical education, we read, is bedevilled by the fragmentation of its curriculum, by the irrelevance of its arrangement, by its examination system, by the authority of extramural professional bodies who can impose their will upon the universities, and by the tendency of teaching hospitals to lose their facility for the undergraduate education of medical students and to become places for the training of specialists. Educational reforms, we are told, do not come from committees, councils or conferences; they arise only from experiment, proof and example. The suggestions on education go no further than the following—that universities should experiment in arranging their undergraduate medical curriculum in various ways, one of which should be to shorten it to not more than four years; that examinations should be designed and used to test the methods of education and not as ends to which the education is directed; that the last two preregistration years of a student's practical training should be free from the interference of examinations in primary and non-clinical subjects. Here is plenty of food for thought by those interested in medical education. In the second suggestion which deals with family practice, we read that infection in the first year of life is almost an expression of family infection, and yet the investigators were surpised how rarely the doctor, the health visitor, the specialist or the parents appeared to consider the problems of health and sickness in family terms. The conclusion is stated, first and foremost, that the intelligent care of children requires one doctor for the whole family—in fact, requires a family doctor. The investigators making this report entirely reject the view which is held elsewhere that the home care of children should be in the hands of separate pædiatric practitioners. Such a development is not, they declare, in the best interests of family life and domiciliary practice in Great Britain. In the three remaining groups of suggestions, the family doctor and the local health authority are mentioned; the local health authority and health visitors are referred to and economy of cooperation is also mentioned. The last of these, the economy of cooperation, must be left to the imagination of readers.

Current Comment.

THE STATE OF THE PUBLIC HEALTH IN GREAT BRITAIN.

In a recent issue a good deal of space was given to consideration of Part 1 of the report of the Ministry of Health of Great Britain for the year ended December 31, 1953. Part 2, which bears the title "On the State of the Public Health", is the annual report of the Chief Medical Officer of the Ministry for the year 1953. Some of the features of Part 2 should be made available to readers of this journal that they may gain a more complete idea of what is happening in Great Britain than reference to the first part of the report will convey. The principal medical officer, Sir John Charles, writes a long introductory chapter. A great deal of the information required will be found in this chapter. He begins with an optimistic statement that 1953 will be remembered as the Coronation Year and that it marked the end of the post-war period and the resumption of more settled conditions of life. Later on he states that many of the basic statistics given in the report seem to be attaining a stability which would "provoke our interested questioning". It might even be suggested, he goes on, that the gains likely to be yielded by the currently available means of improving health have been almost fully achieved. Within the general pattern he finds some subsidiary trends which are satisfactory, and others which give rise to some anxiety. On the credit side is the present level of the birthrate, which is "high enough for the replacement of the population". Further, owing to the great reduction in the mortality from tuberculosis which has occurred in recent years, the death rate for young women aged fifteen to nineteen years has been halved since 1949. Other noteworthy advantages are the virtual disappearance of typhoid fever as a public health problem and the practical elimination of diphtheria within a decade. On the debit side, Sir John Charles traces "the mysterious and inexorable march of cancer of the lung" which continues to claim an additional thousand victims each year; again, the slow reduction in the stillbirth rate leads to the suspicion that a new examination of the problems associated with childbirth is required.

In discussing statistics, Charles amplifies remarks made in the chapter dealing with vital statistics for 1953. This is a field in which he thinks misconceptions are likely to be frequent. One of the commonly held fallacies is that as time goes on the proportion of the population in the normal working ages will be materially reduced. He thinks that while this proportion may in fact become slightly smaller, the main long-term change to be expected is that there will be, on the one hand, more old people and on the other fewer children in the population. He thinks that Britain is approaching the age distribution to be expected in a stationary population with relatively low mortality. The main implications of this change for the health services is fairly clear. "The burden of ill health in old people can be exceedingly heavy, but in taking steps to alleviate that burden by appropriate preventive care and rehabilitation we can also ensure that the resources of the health services are not unduly strained." One factor contributing to the changes in the age distribution is the rapid decline in the birthrate since the beginning of the century; the other main factors are the greatly increased expectation of life for the infant at birth, the contemporaneous and accelerated fall in the infantile mortality rate and the remarkable decline in mortality among children at later years. In regard to the increased expectation of life, this does not mean that

old people are living much longer; any impression that they are is a misconception which is not borne out by the statistics. Thus, in 1838 to 1854 the expectation of life at sixty-five years of age was 10·8 years; in 1952 the expectation was 12·0 years. Old people are not living appreciably longer. What is happening is that many more are now attaining the age of sixty-five than formerly, and it is only in this sense that Britons are becoming an older population. There is still a very long way to go before Britons become a nation of centenarians.

The notifications of scarlet fever were fewer than in 1952, measles and whooping-cough have been on the increase, and influenza was more prevalent in 1953 than in 1952. Generally speaking, influenza was a disease of the first quarter of the year and varied greatly in its killing power according to the type of virus. The number of cases of poliomyelitis and of deaths caused by it were more numerous than in 1952; the disease, as in other countries, is manifesting a shift in its incidence from the younger age group to the later groups, but the significance of this change is not yet apparent. Typhoid fever has continued its decline, as has paratyphoid fever. Dysentery registered another of its inexplicable increases.

For the fifth year in succession a substantial decline in tuberculosis mortality was recorded. Deaths from tuberculosis in 1953 were only 40% of what they were in 1948. The number of new cases diagnosed also showed a slight decrease. Further, examination of contacts, though it has been steadily extended, has yielded a smaller proportion of declared infections. It has yet to be determined whether this reduced yield represents a true fall in the incidence of tuberculosis or whether a more intensive search among more carefully selected contacts might be more productive. It is important to note that one of every twelve new cases during the year was detected by examination of contacts and one out of every five by mass radiography. In regard to the treatment of tuberculosis, reference is made to an interim report published by the Medical Research Council on the chemotherapy of the disease. It was found after three months' treatment that isoniazid was an effective drug in pulmonary tuberculosis, but that given alone it was not more effective than streptomycin *plus* PAS. At the same time, the emergence of bacillary resistance was a most serious problem. In the spring of 1953 a second report appeared, and it was found that streptomycin *plus* isoniazid was clinically the most effective combination. At the same time, it was urged that none of the three drugs mentioned should be used by itself, nor should two of them be used in combination for a patient whose organisms were already resistant to one of the pair. In regard to bacterial resistance, it was found that streptomycin *plus* isoniazid was quite as effective as streptomycin *plus* PAS in the prevention of the emergence of bacterial resistance. Another report was concerned with a comparison of treatment with streptomycin *plus* isoniazid and PAS *plus* isoniazid respectively. It was demonstrated that PAS *plus* isoniazid ranked with the most efficacious combinations so far tested and possessed the advantage that both drugs were administered by mouth. No mention is made in the report of the provision of financial allowances to sufferers from tuberculosis.

Cancer is discussed. It is pointed out that the term "cancer services" is a misnomer in that the diagnosis and treatment of cancer are not one specialty with a service of its own. No accurate evaluation of the achievements of what are known as cancer services is possible until the incidence of cancer is known. There is a scheme of voluntary registration which was devised in order that the incidence might be learned, but so far the information has been obtained largely from the records of radiotherapy departments only and for this reason is not representative of cancer in all its manifestations. The mortality from cancer as a whole showed a slight increase during the year, although the number of deaths of females had fallen. The increase was caused mainly by the number of deaths of males attributed to cancer of the lung. This disease predominantly affects men in their middle or later years and now constitutes 25% of all male deaths from cancer. The ratio of female to male deaths from lung cancer is no more than one to five and a half.

A good deal of space is given to discussion of the education of the public in the methods of individual and community health preservation. The onus of educating the public is placed chiefly on the staff of the Health Department. It is pointed out that success is more likely to be attained if instruction is confined to one particular topic according to the circumstances of the moment. The occurrence of home accidents seems not to be susceptible to preventive treatment. The number of deaths from this cause has varied little from year to year, and as usual those at the extremes of life are the principal victims.

The last subject to be mentioned in this report is the setting up of a clinical research board by the Medical Research Council. Sir John Charles states that there is now an opportunity altogether greater than before to broaden the basis of clinical research in Great Britain and to give it an appropriate measure of central encouragement.

CHOLESTEATOMA OF THE MIDDLE EAR.

A GREAT DEAL of painstaking work has gone into the preparation of a recently published monograph on cholesteatoma of the middle ear by Lars Winderen and Johannes Zimmer.[1] The study, which comes from the departments of oto-laryngology and radiology of the University Hospital in Oslo, is based on a review of 536 ears with chronic middle ear infection; special regard has been paid to the finding at operation of cholesteatoma in the middle ear and its vicinity, the term cholesteatoma being used in a limited sense. The term has in fact been used in medical literature in a number of ways. According to H. C. Ballenger and J. J. Ballenger[2] three types of cholesteatoma have been described. The primary or true cholesteatoma, which is extremely rare, is the result of an embryonic rest. Secondary cholesteatoma is the one usually seen and follows chronic otitis. It is the result of an invasion of epithelium from the external auditory canal into the middle ear through a marginal perforation. The third type results from an ingrowth of epithelium from Shrapnell's membrane without a preexisting perforation or *otitis media*. Winderen and Zimmer are concerned only with the secondary type, which they describe as pseudocholesteatoma or false cholesteatoma, and they quote the definition of Young: "A smooth-walled silvery cyst, lying in a bony cavity and easily detached from its bed. The cyst wall consists of concentric layers of epithelium, the parietal surface actively growing and shedding squames, so that the wall is a series of successive layers." Winderen and Zimmer state that the "cyst" contains scales, mycelia and cholesterol crystals originating from the breaking-down of epithelial elements and suppuration. With the increasing content of these elements the "cyst" expands and "grows".

The monograph has two parts dealing respectively with clinical and radiological aspects, but naturally the two are merged in places. From a clinical point of view, emphasis is laid on the indications for surgical intervention in middle ear infection, but attention is also paid to some other of the problems encountered, such as the incidence of otogenic complications, the duration of aural discharge and the time of its onset, the cell system and especially the degree of pneumatization and its relation to the factors mentioned, the type of ear drum perforation and the sedimentation rate. From the radiological point of view, consideration is given to the correspondence between the X-ray and operation findings as well as to the incidence of failure in X-ray diagnosis. Attempts have also been made to elucidate the problems involved in the X-ray differentiation of chronic middle ear infection with and without associated cholesteatoma.

[1] *Acta radiol.*, Supplement 111, 1954.

[2] "A Manual of Otology, Rhinology and Laryngology", Lea and Febiger, 1954, page 290.

The total of 536 ears studied belonged to 523 patients. In the operation group, X-ray findings and reports were compared with the operation findings in 132 cases of chronic *otitis media* associated with cholesteatoma, and in 45 cases of chronic *otitis media* without cholesteatoma. In addition to these, operation was carried out on 29 suppurating ears with cholesteatoma and 18 suppurating ears without cholesteatoma not subjected to previous X-ray examination. The presence of cholesteatoma was demonstrated in 65% of the ears with chronic *otitis media* subjected to surgery. There was no evidence of its presence in the other 35%. One half of the patients were operated on before the age of thirty years, the other half after that age. Winderen and Zimmer remark that this accords with the conservative attitude in relation to treatment previously adopted by most otorhinologists in Norway. Serious complications were observed in 56% of the cases associated with cholesteatoma and in 48% of those in which it was not present. This gives a total incidence of 54% of serious complications in the operation cases. Of the cases of chronic otitis with cholesteatoma in which operation was performed, marginal perforation of the drum membrane was demonstrated in 97%, and in those without cholesteatoma it was found in 81%. Operation consequently failed to disclose cholesteatoma in 32% of the cases with marginal perforation, despite a history of prolonged suppuration. From all the evidence that they have collected, Winderen and Zimmer state that it seems justifiable to conclude that in the case of chronic *otitis media* with marginal perforation and aural discharge of ten to twenty years' duration, the likelihood of serious complications is so great that operative treatment should be advised.

In relation to the development of the cell system of the temporal bone, Winderen and Zimmer present a number of interesting findings and deductions. On the question of arrested development or sclerosis of the cell system associated with chronic suppurative *otitis media* and chronic mastoiditis there have always been two schools of thought. The first holds that the sclerosis is the result of chronic inflammation, and the second that the sclerosis is the predisposing cause of chronic inflammation. Winderen and Zimmer's findings led them to subscribe to the first of these two schools. They also found that the more highly developed the cell system was, the shorter was the duration of the discharge. On the other hand, complications were common in cases with such cell systems. It was also found that complications occurred more often when the cholesteatoma involved the antral region, and their incidence increased with the size of the cholesteatoma.

The radiological section of the monograph takes up more than half the publication, but it is not necessary to examine this in detail now. It will be of interest to radiologists, but the conclusions are, on the whole, confusing. Two main points emerge. The first is that X-ray examination provided less accurate information in cases of *otitis media* without cholesteatoma than in cases in which cholesteatoma was present. The second is that X-ray diagnosis relating to the presence or otherwise of cholesteatoma does not always accord with the clinical diagnosis and so needs to be approached with reserve.

This monograph has been carefully prepared and is freely illustrated, especially in the section on radiology. In general, the conclusions which it offers are not new, but they do serve to establish more firmly conceptions already held.

URINARY CALCULUS AND THE CONTROL OF PROTEUS INFECTION.

BACTERIAL INFECTION is well known to be a factor in the formation of urinary calculi. E. S. J. King[1] has pointed out that it produces its effects in a number of ways. It gives rise to a nucleus, which may be a clump of organisms, desquamated cells, pus or inspissated mucin from epithelial secretion. Bacterial activity often produces a gross alteration in pH. There is usually a considerable increase in the amount of protein in the fluid, and as a result of the pH change this may be precipitated. The alteration of pH will also cause considerable change in the crystalloids. These changes will become effective in the region of nuclei or of calculi which have already formed. Thus infection may be the initiating factor in calculus formation, or it may be responsible for precipitation of material on the surface of a calculus and therefore for increase in its size. Apart, however, from these general results of infection, *Proteus vulgaris* is considered to play a particular role in stone formation by virtue of its urea-splitting property. With this in mind, C. W. Vermeulen and R. Goetz[1] carried out some interesting experiments with an anti-bacterial agent, retrofurantin (used in the form of "Furadantin"). This is stated to be of value in combating urinary infection with a number of organisms, including *Proteus vulgaris*, that have not been readily suppressed by other agents. The experiments were carried out on white rats. Into the bladder of each a foreign body was inserted by open operation; it was designed to become the nucleus of a calculus. The foreign body, which was a piece of zinc, had been immersed in a broth culture of *Proteus vulgaris* before being inserted into the bladder. Vermeulen and Goetz state that when Proteus infection is introduced in the urinary system in this manner, few untreated animals will survive for more than three weeks. The effect of "Furadantin" was, however, striking. In a controlled series of rats, 16% of untreated animals survived for three weeks, but 67% of animals survived for this period if treatment was begun three days after introduction of the infection. Large doses were used for these rats—namely, 90 milligrammes of "Furadantin" per kilogram each day, the powdered drug being mixed with the food; fluids were freely available. Vermeulen and Goetz state that the dose used for the rats was about nine times that used at present for human beings when calculated weight for weight. Experiments are in progress to determine if smaller doses will prevent deep parenchymal infection of the kidneys, as the larger doses were shown by examination of tissue sections to have done. The clinical possibilities remain to be explored; but it may be reasonably hoped that if "Furadantin" will indeed control urinary infection with *Proteus vulgaris* it will help to remove a potent factor in stone formation.

[1] M. J. AUSTRALIA, June 21, 1952.

[1] *J. Urol.*, August, 1954.

THE FOCLA ANNUAL POST-GRADUATE COURSE.

CONCERN is sometimes expressed that the medical profession, particularly the organized profession, is unduly occupied with medico-political questions at the expense of the advancement of medical science. It is reassuring, therefore, as well as stimulating, to note the enthusiasm with which an important section of the New South Wales Branch of the British Medical Association—namely, the Federation of Country Local Associations (known as FOCLA, in the modern fashion)—has established and built up its annual post-graduate course. The fourth such course, which is to be held at Wollongong from March 14 to 18, 1955, has a particularly attractive programme. Details will be published in the near future, but it may be mentioned that speakers will include Dr. R. A. Kern, of the United States of America, and Professor H. Messel, of the University of Sydney Physics Department. An outstanding group of clinicians and teachers from Sydney and Melbourne will contribute individually from their special knowledge. Dr. H. H. Lee, of Wollongong, will speak on the medical history of the Wollongong district. The R. D. Mulvey Memorial Oration, commemorating a notable former member of FOCLA, will be delivered by Dr. K. C. T. Rawle, of Orange. A variety of social events complete the programme. The president of FOCLA is Dr. B. A. Cook, of Bulli, the secretary is Dr. Adrian Paul, of Gosford, and the course secretary is Dr. J. D. Maude, Church Street, Wollongong.

Abstracts from Medical Literature.

PATHOLOGY.

Endometriosis of the Umbilicus.

E. S. J. KING (*J. Path. & Bact.*, April, 1954) has recorded seven new cases of endometriosis of the umbilicus. In each a nodule lay immediately under the skin of the umbilical fossa and in no case involved the peritoneum. In almost all cases hæmorrhage occurred externally and developed at an early stage in the clinical history. Histologically, the endometrial glands were found to communicate with the surface through the epidermis. There was an increase in the number of sudoriferous glands round the periphery of the nodule, and in some cases this was particularly prominent. In some, the distinction between the endometrial and sudoriferous glands at the margin of the nodule was not clear. The main hypotheses relating to the development of endometriosis are briefly considered, and it is concluded that the epigenetic hypothesis is the most satisfactory. The author shows that one special form of this hypothesis as applied to endometriosis, namely the peritoneal hypothesis, is unsatisfactory for at least many cases of umbilical endometriosis. He states that one of the factors in the development of endometriosis is ovarian hormonal activity. Such hormones are known to affect the skin, and in these cases it appears that they affect the periumbilical skin by increased formation of sudoriferous glands, but that the tissue of the umbilical fossa itself is affected differently and gives rise to endometrial tissue.

Renal and Cerebral Lesions in the Tuberous Sclerosis Complex.

KEITH INGLIS (*Am. J. Path.*, July-August, 1954) submits evidence in support of the hypothesis that (*a*) the renal tumours of the tuberous sclerosis complex constitute a distinctive tumour *sui generis* and (*b*) the renal tumours of the tuberous sclerosis complex, like the cerebral nodules, are of neural origin, the cells of the cerebral nodules having arisen from the neural tube, and the essential cells of the renal tumours from the neural crest.

Primary and Secondary Ovarian Adeno-Acanthoma

MALCOLM B. DOCKERTY (*Surg., Gynec. & Obst.*, October, 1954) presents data from 40 cases of ovarian tumours which exhibited the unusual picture of adeno-acanthoma. The incidence of the lesion was 2%. In 13 cases in which the lesions were designated as primary, the presence of endometrial carcinoma was excluded. In 27 cases ovarian involvement could possibly have been metastatic from a primary endometrial neoplasm. Although the lesions in these 27 cases were designated as secondary for the purposes of this paper, the endometrial growths could well have represented independent foci of neoplasia. In a fair proportion of secondary cases evidence favoured an interpretation based on metastasis from ovary to endometrium. Both primary and secondary ovarian adeno-acanthomata appeared to affect women in young age brackets and were associated with an increased incidence of infertility. Pathologically, the tumours resembled endometrial, rather than ovarian, cancer, and in both groups of cases they were very frequently associated with pelvic endometriosis. In two instances ovarian adeno-acanthomata could be traced in point of origin to such foci. Prognosis was good for patients in both groups, and was surprisingly so in respect to secondary ovarian adeno-acanthomata, which by definition comprised lesions with endometrial as well as ovarian involvement.

Periarteritis Nodosa in a Week-old Infant.

RALPH J. JOHANSMANN AND PEARL ZEEK (*Arch. Path.*, September, 1954) report a case of widespread, acute *periarteritis nodosa* in a week-old infant. They state that the lesions apparently developed after birth and followed massive but incomplete renal infarction, the latter being caused by embolism from a thrombus in an aneurysm of the *ductus arteriosus*. The vascular lesions in this case appeared to be identical in morphology, distribution and stages of lesions represented with the necrotizing arteritis produced experimentally in rats by many investigators who have employed procedures which caused renal ischæmia and rapid rise in blood pressure. The various stages of the lesions in this case have been produced in rats within a similar period of seven days. This case refutes the belief that the rat type of *periarteritis nodosa* does not occur in man.

Hyaline Arteriolar Sclerosis.

P. O'B. MONTGOMERY AND E. E. MUIRHEAD (*Am. J. Path.*, May-June, 1954) state that a histochemical characterization of the hyalin of arteriolar sclerosis of benign hypertension has demonstrated the presence of lipids, carbohydrates, free carbonyl groups, protein-bound sulphydryl groups and free potassium. Since similar compounds have been identified in normal smooth muscle, it is likely that the compounds identified in the hyaline substance take their origin from the smooth muscle of the media. An apparent increase of concentration of some of the ingredients (lipids, carbohydrates and potassium) in hyalinized arterioles as compared to normal arterioles is considered to result, in all probability, from unmasking of these substances due to an alteration in their physico-chemical state during the process of hyalinization. The suggestion is made that the subendothelial location of hyalin in some instances results from the flow of hyalin of medial origin through the fragmented internal elastic membrane to a subendothelial location. The authors state that the hyaline lesions of benign arteriolar sclerosis differ histochemically from the previously reported acute arteriolar lesions of malignant hypertension only in the absence of acid phosphatase. Hyalin is considered to result from an alteration of the smooth muscle of the media of the arteriole.

Renal Changes in Eclampsia.

A. D. TELFORD GOVAN (*J. Path. & Bact.*, April, 1954) describes the histology of the kidney in 33 cases of fatal eclampsia. Glomerular changes were the most prominent feature. Endothelial-cell proliferation, often locally distributed, was common in all cases. The mesangium was increased, owing apparently to the expansion of the intercapillary space, and irregular swelling of the capillary basement membranes on their mesangial aspect was also noted. Occlusion of capillaries occurred in a proportion of the glomeruli in all cases. Hyaline droplets were found in the mesangium and glomerular epithelium, as also in the epithelium of the first convoluted tubules. Subendothelial hyaline deposits were present in the afferent arterioles and some of the cortical arteries. Similar changes to those mentioned above were found in the kidneys of 12 patients who died from non-toxæmic disease during pregnancy. The author suggests that many of the changes hitherto ascribed to hypertension may be the result of endocrine activity.

Gastric Carcinoma.

R. M. MULLIGAN AND R. R. REMBER (*Arch. Path.*, July, 1954) state that a study of 138 cases of gastric carcinoma resulted in the establishment of three major histological types with characteristic biological behaviour — namely, mucous cell carcinoma, pyloro-cardiac gland cell carcinoma and intestinal cell carcinoma. Mucous cell carcinoma has the following features: frequent growth as signet-ring cells with mucin production or as undifferentiated cells, but uncommonly as differentiated glandular structures; significant onset before forty years of age; primary tumour appearing as a relatively large, flat, diffusely infiltrative growth, and a high incidence of extension and metastasis. Pyloro-cardiac gland cell carcinoma is characterized by the following features: formation of well-differentiated glandular structures; significantly high incidence in males; onset usually after forty years of age; localization preponderantly in antrum and cardia; primary tumour appearing usually as a delimited, fungating, sometimes widely ulcerated growth, and a diminished tendency for extension and metastasis as compared to mucous cell carcinoma. Intestinal cell carcinoma displays the following traits: two growth patterns with interplay in some tumours or in double primary tumours, the first well differentiated glandular and the second mainly undifferentiated; a suggestively greater incidence in females than the other two types of gastric carcinoma; onset usually after forty years of age; significant localization in the fundus; high frequency of pernicious anæmia; primary tumour appearing as a polypoid, a fungating, or a relatively flat, nodular, delimited growth, with a low propensity for extension and metastasis. Although all three types of gastric carcinoma extend, metastasize and kill, the approximate degree of lethality as

determined both at autopsy and by survival following gastric resection is as follows: mucous cell carcinoma 98%, pyloro-cardiac gland cell carcinoma 75%, intestinal cell carcinoma 60%. A valuable adjunct to the future study of gastric carcinomata, especially those of the pyloro-cardiac gland cell and the intestinal cell types, would be the application of elastic tissue stain to determine the relationship of vein invasion to survival and to the dissemination of metastases, notably to the liver. Less radical gastric resection is probably indicated for mucous cell carcinoma, since prognosis is so poor even with the most radical total gastrectomy technically possible. Depending on the case, radical gastrectomy of variable totality is indicated for pyloro-cardiac gland cell carcinoma and intestinal cell carcinoma. In patients with signs of local recurrence at the anastomosis site following gastric resection for either of these two types of carcinoma, an attempt at secondary resection seems warranted. The similarity of the growth patterns of pyloro-cardiac gland cell carcinoma and of the endometrial glands during the menstrual cycle suggests the use of hormones, such as androgens or œstrogens, in treatment of recurrent or metastatic carcinoma. Further analysis of more cases of gastric carcinoma should be made by study of histological features and biological behaviour to confirm or refute the observations described.

Giant-Cell Tumour of Bone.

ROBERT R. WILLIAMS, DAVID C. DAHLIN AND RALPH K. GHORMLEY (*Cancer*, July, 1954) state that true giant-cell tumour is a distinct neoplasm with well-defined histological criteria. It is important to distinguish its "variants", such as non-osteogenic fibroma, bone cyst and aneurysmal bone cyst. The authors report a study based on 101 cases of true giant-cell tumour of bone. About 68% of the patients were in the age group twenty to thirty-nine years. Nearly 10% of the patients were less than twenty years of age. There was a slight predilection for the female sex. The lesions were situated in the epiphyses of long bones of the limbs in more than 80% of cases and about the knee in approximately 60%; the ilium and sacrum were involved in some 14%. Trauma could not be implicated as a stimulus for the formation of giant-cell tumour. The average duration of symptoms before diagnosis was one year, with variation from ten days to seven years. A mass was palpable in most of the patients. The authors state that the necessity for adequate amounts of tissue for exact diagnosis cannot be too strongly stressed. Needle biopsy of bone tumours frequently proves unsatisfactory for accurate histological diagnosis, largely because malignant portions may be missed. The variants of giant-cell tumour may be difficult to recognize even with an ample specimen. Although this type of tumour is frequently composed of giant cells and stromal cells, variable amounts of fibrosis and osteoid formation may be observed especially within those tumours altered by previous treatment or fracture. Focal areas of xanthoma cells are not infrequently seen. Grading of the tumour as a guide to prognosis has not been of value in the experience of the authors. Malignant transformation occurred in eight of the cases of giant-cell tumour after an appreciable interval following the original histological diagnosis. In two other cases, mixed areas of giant-cell tumour and fibro-sarcoma were observed at the initial examination. Further observations are indicated to clarify the relationship of giant-cell tumour. The results indicate that irradiation does not reduce the incidence of recurrence in cases of giant-cell tumour and perhaps introduces the hazard of irradiation-induced sarcoma.

MORPHOLOGY.

Relation between Levels of Dietary Protein and Skeletal Growth.

A. M. FRANDSEN *et alii* (*Anat. Rec.*, June, 1954) found that skeletal growth and endochondral ossification were strikingly decreased by low protein intake resulting either from a low level of dietary protein or from a decreased intake of diets containing a normal amount of protein. Invariably the protein-deficient animals were more severely affected than the corresponding pair-fed controls. Histological studies of the proximal tibial epiphysis revealed the following changes which were again more severe in deficient animals than in pair-fed controls: decrease in width of the epiphyseal cartilage plate due to diminished number and size of cartilage cells; increase in cartilage ground substance; slowing down and final arrest of cartilage erosion and bone formation, resulting in fewer and coarser bony trabeculæ. Variable amounts of fat in the bone marrow were noted. The most extreme changes were shown by animals on the 0% casein diet, which resulted in "sealing-off" bone and the virtual absence of fat cells in the marrow.

Anatomy of Cirrhosis.

W. S. HARTROFT (*Anat. Rec.*, May, 1954) found that the distribution of fibrous tissue in the initial stages of cirrhosis in choline-deficient rats was clearly non-portal. In later stages, trabeculæ extend around large branches of the portal vein in an apparently haphazard fashion. Thick slices (100 to 200μ) of ink-injected livers were prepared from rats sacrificed at intervals up to sixteen months from the time they had been put on one of several choline-deficient diets. From observations of the lesions in these special preparations, as well as in ordinary microsections, the pathogenesis of late stages of the cirrhosis was correlated with the early stages. The author states that parenchyma adjacent to large conducting branches of the portal vein, although periportal in a geographic sense, is non-portal in the functional use of the term, because tissue in these situations is not supplied by sinusoids which arise directly from the vein. Much of the tissue around large conducting vessels is supplied by blood that reaches it from terminal portal venules *via* sinusoidal pathways of appreciable length. From annular, non-portal trabeculæ which link neighbouring central veins, fibrous bands extend toward large branches of the portal vein, following pathways midway between terminal portal venules, thereby replacing the functionally non-portal tissue in these regions. By a continuation of this process, the regions around conducting portal veins become fibrotic. When this stage in the development of the cirrhosis has been reached, although the fibrosis is geographically periportal, it can still be regarded as functionally non-portal. By trabecular isolation of the parenchymal masses around terminal portal venules, "Rappaport's structural unit" is dissected and its boundaries are delineated. "Rappaport's structural unit" comprises portions of all those hexagonal lobules which lie along the course of any one terminal portal venule and is smaller than a single lobule. Without this concept of the organization of the hepatic architecture, the pattern assumed by the fibrosis would be difficult to comprehend. The terminal portal venule is regarded as the essential landmark for the lobular orientation of hepatic lesions. The relations of this vessel and its morphological characteristics are illustrated. The author states that the cirrhosis associated with chronic alcoholism in man is believed to be periportal in a geographic sense only, for the terminal portal venules in these livers are non-fibrotic.

Human Corpus Callosum.

J. TOMASCH (*Anat. Rec.*, May, 1954) gives the results of a study of the number and size of the fibres of the *corpus callosum*, as well as an account of the literature on the present state of exact knowledge concerning this structure, and draws attention to the divergence of opinions on most of the important questions and problems related to it. He states that it is certainly more than a strict commissural system connecting corresponding parts of the cortex in both hemispheres. The number of fibres in the *corpus callosum* examined varied from about 177,000,000 to 193,000,000, of which the myelinated fibres number 106,000,000 to 112,000,000, and unmyelinated from 65,000,000 to 87,000,000. In one brain the number of myelinated fibres was relatively low and the number of unmyelinated relatively high. As the total number of neurons in the cortex is about 10,000,000,000, the number of callosal fibres is less than 2% of the fibre connexions of the cortical neurons.

Vascular Relations of Pancreas.

L. L. OLSEN AND R. T. WOODBURNE (*Surg., Gynec. & Obst.*, December, 1954) state that there is a general pattern in the network of arteries about the pancreas, which is formed from eight major vessels. Arterial arcades on the anterior and posterior surfaces of the head of the pancreas represent arterial shunts between the hepatic and superior mesenteric arteries. There are usually two superior and two inferior pancreatico-duodenal arteries. Most of the major vessels of the pancreas course on its dorsal aspect and are not readily accessible anteriorly. The arteries of the pancreas are accompanied by veins, located more superficially.

Clinico-Pathological Conferences.

A CONFERENCE AT SYDNEY HOSPITAL.

A CLINICO-PATHOLOGICAL CONFERENCE was held at Sydney Hospital on September 21, 1954, the medical superintendent, DR. NORMAN ROSE, in the chair. The principal speaker was DR. R. J. WALSH, Director of the New South Wales Red Cross Blood Transfusion Service.

Clinical History.

The following clinical history was presented.

The patient died at the age of thirty-eight years after being treated for nine years at Sydney Hospital for what was thought to be idiopathic aplastic anæmia. During that time he was given about 50 transfusions, probably 200 bottles of blood.

All his life he had been anæmic and treated with iron. The only other illnesses he had had were measles, chickenpox and a broken arm; and except for his mother, who had diabetes controlled by diet, his family was healthy. He had worked as a ticket writer and as a baker. He had his first transfusion at the age of twenty-nine years. At that time there were no abnormal physical signs other than those associated with anæmia, and no cause for his condition could be found. Examination of the blood showed a hæmoglobin value of 33% and a total of 1,180,000 red cells per cubic millimetre (marked anisocytosis, macrocytosis, microcytosis and poikilocytosis were noted, and 0·7% of reticulocytes were present). The total leucocyte count was 3100 per cubic millimetre, made up of 48% neutrophile cells, 49% lymphocytes and 3% monocytes. There were 293,000 platelets per cubic millimetre. The colour index was 1·13. The blood group was O (IV), Rh-positive. There was no free acid in the stomach at a test meal examination, but no histamine was given. On several occasions occult blood was detected in the fæces. The results of all other tests were normal—urinalysis, microscopic examination of fæces, basal metabolic rate determination, X-ray examination of the chest, gastro-intestinal tract and long bones, blood Wassermann and Kline tests, determination of blood proteins, urea and bilirubin contents and tests for lead and arsenic poisoning.

During the first five years his need for transfusions increased till he was having ten or more each year. The anæmia was severe, leucopenia was persistent, and platelets were usually reported as scanty. Erythrocyte fragility was normal (commenced at 0·45%, complete at 0·3%). The serum bilirubin content was 0·5 milligramme per 100 millilitres. The plasma protein values, blood sugar content and glucose tolerance curve, and results of thymol turbidity test and urine examination were normal. Sigmoidoscopy and barium meal X-ray examination showed no lesions. The liver appeared to be enlarged in the X-ray films, and a biopsy of skin showed deposits of iron. The sternal marrow was examined on two occasions and found to be almost normally cellular, erythropoiesis was normal with many young forms present, granulopoiesis showed a shift to the left but was otherwise normal, and megakaryocytes were present in increased numbers. Iron pigment and lymphoid follicles were present.

At this stage splenectomy was performed. In the remainder of the patient's life his transfusional requirements were less (about four transfusions each year), and his white cell count became normal or high. Platelets were plentiful and normoblasts numerous.

The third and terminal phase of the patient's illness commenced about three months before he died. He developed weakness, anorexia, polydipsia, sugar and acetone in his urine and a blood sugar content of 410 milligrammes per 100 millilitres of blood. By this time his skin was slate grey, pigmentation was very marked in scars and creases, the liver was hard, nodular and enlarged, and the penis was small. The result of a direct Coombs test was negative, the serum bilirubin content was less than 0·2 milligramme per 100 millilitres, and in twenty-four hours he excreted 46 milligrammes of urobilinogen in the fæces and 7·2 milligrammes in the urine. The serum iron content was 250 grammes *per centum* and the glucose tolerance curve was diabetic. Biochemical investigation revealed a plasma content of albumin of 3·8 grammes and of globulin 2·1 grammes per 100 millilitres. The thymol turbidity value was six units. The serum content of sodium was 122 milligrammes and of potassium 4·9 milligrammes per 100 millilitres, and the carbon dioxide combining power of the blood was 21·5 milliequivalents per 100 millilitres. There was no change in the eosinophile cell count after an injection of ACTH. In the Kepler-Power test the night urine exceeded the day urine and the Kepler index was 26 (an index less than 25 indicates adrenal insufficiency). The ketosteroid excretion in twenty-four hours was 6·5 milligrammes. The diabetes was treated with diet and soluble insulin (52 units per day). The patient had several attacks of hypoglycæmia and inconstant cardiac irregularities ranging from complete heart block to auricular fibrillation. At times he showed extreme breathlessness and venous engorgement. Treatment included a salt-free diet and digitalis. The possibility of Addisonian crises was considered and dismissed on clinical grounds.

The story of this patient is presented for the problems it poses, not of diagnosis so much as of understanding the more fundamental disturbances.

Clinical Discussion.

DR. R. J. WALSH: It is not difficult to diagnose the cause of the patient's death, because it is apparent that he died from hæmosiderosis or exogenous hæmochromatosis. This developed as a result of the therapy of the initial anæmia, and the blood transfusions which apparently kept him alive for a long time eventually caused his death.

There are many interesting aspects which could profitably be discussed. In the available time I am proposing to limit my remarks to a consideration, firstly, of the nature of the anæmia and, secondly of the effects of the hæmosiderosis on the function of various organs. The discussion will be more concerned with physiology than with pathology and will emphasize pathogenesis rather than clinical features.

The illness commenced with the development of a severe anæmia about nine years before death. The nature of this anæmia was not diagnosed at the time, and in retrospect the diagnosis is not much easier. It is at once apparent that it was not an idiopathic aplastic anæmia as stated in the record. The marrow was examined twice by sternal puncture and on neither occasion was it aplastic, but an inadequate number of cellular elements were formed in the marrow tissue and delivered to the circulating blood. For practical purposes the hæmopoietic tissue was not functioning. Hæmatinic substances were almost certainly supplied in large amounts, but failed to change the marrow picture. The term "refractory anæmia" is more appropriate than "aplastic anæmia".

Why was the anæmia refractory to all forms of therapy? Any answer to this question must be conjectural, because usually the morbid anatomists can neither prove nor disprove a diagnosis. For purposes of discussion it is suggested that the patient suffered from hypersplenism. It is always difficult to diagnose this condition with certainty until the results of splenectomy can be ascertained. It is advanced in this case, however, because: (i) The marrow was normally cellular with an increase in the number of megakaryocytes. (ii) A pancytopenia eventually developed. The red cells were affected at the onset of the illness; later the white cells and platelets were also affected. (iii) There was an obvious improvement in the peripheral blood picture after splenectomy, and the transfusion requirements of the patient were apparently reduced to less than half.

Two arguments which may be advanced against a diagnosis of hypersplenism are:

1. The fact that splenectomy produced improvement but not cure. I feel that the continued anæmia was probably the result of excessive iron deposition in the marrow tissue, a point which will be discussed later. It may also have been due to residual accessory spleens not discovered at operation.

2. The macrocytic type of the peripheral blood picture. Only one blood count is given in the history, and no mention is made of a macrocytic type of bone marrow. Was the blood picture persistently macrocytic? Even if it were so, the diagnosis of hypersplenism is not invalidated, because slight macrocytosis is not unknown in patients whose anæmia has been completely cured by splenectomy.

What is the mechanism of hypersplenism? Two theories are currently and ardently held by different schools. The first contends that the maturation and delivery to the circulation of cellular elements—red cells, white cells and platelets—is controlled by the spleen through the agency of humoral substances. In hypersplenism there is excessive secretion of these hypothetical substances resulting in an arrest of maturation in the red-cell precursors (leading to anæmia), in the white cells (producing neutropenia) and in the platelets (bringing about thrombocytopenia and an increase in the number of megakaryocytes). Some observers

have reported that the morphology of the megakaryocytes in these conditions suggests that they do not produce platelets. The reduction in the number of cellular elements in the peripheral blood may concern any or all of the different varieties of cells.

The second theory is that hypersplenism is the result of excessive phagocytic activity of the spleen, producing a deficiency of the formed elements of the blood. The resultant anæmia is associated with reticulocytosis and hyperbilirubinæmia, the neutropenia with a shift to the left of the polymorphonuclear elements, and the thrombocytopenia with an increase in the number of marrow megakaryocytes.

There is not time, nor is this the place, to discuss the merits of the two theories. It is possible that both mechanisms may play a part. In the patient under consideration splenectomy produced a marked improvement of the anæmia with normal numbers of platelets and white cells. It is noted in the history that normoblasts were numerous, and this is not uncommon after splenectomy. Some workers attribute to the spleen the function of controlling denucleation of red cells.

It is apparent from some of the tests recorded in this long illness that a hæmolytic type of anæmia was suspected. However, no evidence has been presented to suggest that hæmolysis was occurring at an increased rate. The findings of pigment studies were normal, there was no reticulocytosis, and the result of a direct Coombs test was negative.

If we turn now to the terminal phase of the patient's illness, it is desired to postulate that a profound disturbance of iron metabolism can explain the symptoms and findings until death. It is, however, necessary to mention briefly some of the more important aspects of iron metabolism.

Iron is probably unique amongst all the substances concerned with the metabolism of the body for two reasons: (i) it cannot exist in the body unless it is bound to protein; (ii) there is no mechanism for excretion of iron other than in negligible quantities in the form of cellular debris. Once iron has passed the mucosa of the gastro-intestinal canal or entered the body by injection, it cannot be lost by physiological processes.

Under normal conditions the amount of iron absorbed from the food equals the amount lost from the body. Absorption occurs mainly in the lower part of the stomach and the upper part of the duodenum and is regulated by mechanisms which are not yet fully understood. From the mucosal cells of the gastro-intestinal tract, iron is transported in the serum to the tissue stores. These stores are mainly in the liver and spleen and contain the iron which can be used for hæmoglobin synthesis in the bone marrow, should the need arise. There are also smaller amounts of iron throughout the body concerned with the metabolism of the cells. This is known as parenchymal iron. As far as is known at present there is no exchange of iron between the available iron stores and the parenchymal iron. The liver and spleen contain approximately 0·75 gramme of iron which is linked to protein. At least two chemical substances, hæmosiderin and ferritin, are involved, and there may be other compounds not yet identified. As it is required, iron is transferred from the stores to the bone marrow by means of the blood and is then utilized for the production of hæmoglobin. The hæmoglobin iron in the red cells of an average adult measures between two and a quarter and three grammes. When they have completed their life span of one hundred and twenty days, the aged red cells are destroyed in an orderly fashion, the oldest being removed first. The reticulo-endothelial cells, especially in the spleen, are the ultimate repositories of aged cells, and the iron of the hæmoglobin is liberated to be stored in the liver and in the spleen until required for further hæmoglobin synthesis. This completes the cycle of iron within the body. It is to be noted that the total iron in the body of an adult is between three and four and a half grammes, and that this amount is reasonably constant in physiological conditions.

It is necessary to say a little about the chemistry of the iron storage compounds. Both are protein complexes, but only hæmosiderin is detected in histological preparations. Hæmosiderin is amorphous, granular and insoluble in water and saline. It stains blue with the Prussian Blue reagent. On the other hand, ferritin is soluble and non-granular, but can be crystallized from solutions. It does not stain with Prussian Blue reagent. The relative amounts of hæmosiderin and ferritin are fairly constant, even in the extremes of iron excess and iron deficiency. Ferritin therefore contributes at least as much as, if not more than, hæmosiderin to the total iron content of the tissues. This fact must be recognized when the amount of iron present in the tissues is assessed from histological preparations.

There can be no doubt that there was an enormous excess of iron in the body of the patient under consideration. The iron had been obtained in three ways:

1. Approximately 200 pints of blood were transfused during the life of the patient; this is equivalent to about 50 grammes of iron.

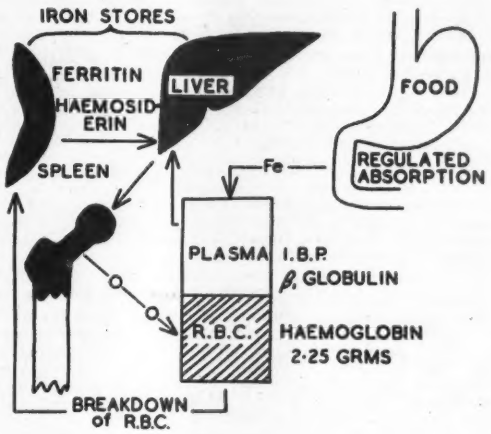

FIGURE I.
Blackboard diagram used to illustrate the essential features of iron metabolism.

2. There is a history that the patient had been treated with iron throughout his early life, and, in accordance with custom, he probably received large amounts of therapeutic iron by mouth during his illness. The regulation of iron absorption in the gastro-intestinal tract is not absolute; for example, it has been shown that a low phosphorus diet allows absorption of increased amounts of iron from food. Dr. Kaldor has shown in our laboratories recently that addition of iron to the normal diet of rats results in increased amounts of iron from food.

3. Dr. Kaldor has shown also that anæmia *per se* increases absorption of iron from the gastro-intestinal tract. This is easy to understand in relation to iron-deficiency anæmia, where there is a need for increased absorption; but it also occurs in other types of anæmia which are not characterized by deficiency of iron, for example, hæmolytic anæmia.

It has been reported that in some cases of transfusion hæmosiderosis the amount of iron in the liver alone exceeds the total introduced by blood transfusion. This is almost certainly the result of excessive iron feeding during therapy and the increased absorption which occurs during the anæmic phase. It is not possible to assess the total amount of iron in the body of the patient, but it would probably be no exaggeration to say that his tissues contained up to twenty times the normal amount.

How does this excessive iron interfere with the metabolism of tissues? Is it by interference with some specific enzyme system, or is the whole cellular metabolism involved? Is it primarily hæmosiderin which is responsible, or is ferritin important? These questions cannot be answered with our present knowledge, but there can be no doubt that an excess of iron causes death of the victim. It is interesting to note that ferritin has been identified as the vasodepressor material (V.D.M.), a substance which produces profound shock. It has been found in the blood of certain patients in the terminal phase of hæmochromatosis. An analysis of the effects of iron excess on the different organs will explain most, if not all, of the observed findings in the patient under consideration.

Portal cirrhosis with disorganization of architecture, fibrosis and hæmosiderin deposition in the Kuppfer cells, in the parenchymal cells and even in the fibrous tissues are the pathological features in the liver. A primary hepatoma is found on autopsy in 10% to 15% of patients who suffer from an allied condition, endogenous hæmochromatosis. This high percentage is too large to be dismissed as coincidental.

I am not aware of the finding of hepatoma in any patient who has died of transfusion hæmosiderosis, but there is no basic reason why this possibility should be discounted. The histological changes produced in the liver result in functional impairment of the organ.

Fibrosis and brown staining due to hæmosiderin are observed in the pancreas *post mortem*. Diabetes frequently develops, as it did in this patient, and in addition there is usually a reduction in the external secretions of the pancreas. This latter disturbance accentuates the condition of hæmosiderosis. Normally the alkaline pancreatic secretions neutralize the acid secretions of the stomach and prevent absorption of iron.

Hæmosiderin deposition in the cardiac musculature and even in the coronary arteries is usually found in patients with hæmosiderosis and presumably by irritation produces a variety of arrhythmias associated with congestive cardiac failure. This appears to have been a prominent feature in the patient's terminal illness.

In my experience, histological preparations of the adrenal gland in hæmosiderosis have suggested that there is not as much hæmosiderin pigment in the adrenal as in other tissues, and that there has not been gross morphological derangement. However, the clinical and biochemical findings recorded in this patient suggest that there was some adrenal insufficiency. This may have contributed to the diabetes, to the genital organ changes and to the skin pigmentation.

Although there is hæmosiderin deposition in the deep layers of the epidermis in hæmosiderosis, the skin pigmentation is due to melanin or a closely related chemical compound, hæmofuscin. Melanin is produced by cells called melanocytes in the epidermal layers and then stored in neighbouring epithelial cells. Melanocytes are undoubtedly under hormonal influence—the pigmentation of Addison's disease, of pregnancy, and of prolonged therapy with ACTH—but in hæmosiderosis the possibility of direct stimulation by hæmosiderin granules in the epidermis must be considered.

There is no doubt in my mind from a study of patients with endogenous hæmochromatosis that excessive hæmosiderin deposits in the bone marrow may interfere with hæmopoietic activity and thus produce varying degrees of anæmia. With removal of iron by regular bleeding, the anæmia of these patients disappears. In the patient with hæmosiderosis there is no reason why the hæmopoietic tissue should be exempt from the general metabolic disturbances which occur in all other tissues. It is essential to the theory that a splenic anæmia occurred in this patient, that the marrow space be found *post mortem* extending into the long bones, and that hæmosiderin be accepted as disturbing the hæmopoietic tissue.

It is noted in the record that the penis was small. It is usual in these cases, as in hæmochromatosis, to observe also testicular atrophy, loss of body hair and feminizing of the pubic hair; subjectively, impotence is a common complaint. The basis of these changes is not certain, but they are usually thought to be the result of liver impairment. It has been shown that the liver inactivates œstrogenic steroids, and that there is an increase of œstrogens in both the blood and the urine of males with impairment of liver function.

The serum iron content towards the terminal phase of the illness was 250 microgrammes. The diagnostic feature of hæmosiderosis and of hæmochromatosis is not a high serum iron value, although a high value is usually found, but the fact that the specific protein in the blood for binding iron is completely saturated. Normally it is about 30% saturated, and complete saturation occurs only in hæmochromatosis and hæmosiderosis.

To sum up, histological examination can neither prove nor disprove the diagnosis of splenic anæmia, but this diagnosis has been advanced provocatively and in the belief that it is consistent with all except one fact in this interesting history. Splenectomy failed to produce complete relief of the anæmia, but cured the neutropenia and thrombocytopenia. This is unusual in true splenic anæmia, but the failure has been explained as the result of iron excess inhibiting the hæmopoietic tissue and possibly associated with liver and adrenal insufficiency.

Iron excess in the form of hæmosiderin and ferritin is advanced as the cause of most, if not all, of the patient's terminal symptoms, signs and biochemical disturbances. It is not known why an excess of iron should interfere with metabolism of the tissues. There is, however, very little doubt that it does do so and that it may produce death in a number of different ways, depending on the organ which is most severely affected.

A philosophical note should be introduced in conclusion. This patient undoubtedly died as a result of the blood transfusions which he received. Is transfusion of patients with incurable diseases, including proven refractory anæmia, justified? A large amount of blood given by voluntary donors is used to prolong life and not to cure. Is this reasonable? In the hope of provoking discussion it is suggested that life-prolonging transfusions can be condoned only if the recipient is thereby able to live a painless, comfortable and ambulatory existence.

DR. A. E. MCGUINNESS: This patient was under my care after the splenectomy, and at the time of operation he was considered, and in my opinion rightly so, as suffering from refractory anæmia. I would agree with Dr. Walsh that there was evidence of hypersplenism or, as Dameshek has pointed out in cases of aplastic or refractory anæmia in which splenomegaly is not noted, splenism. Splenism is not uncommon in refractory anæmia, and after splenectomy, Dameshek has pointed out, there may be clinical improvement for some time in the anæmia. Splenectomy was done on that basis, and the improvement justified the operation.

I would like to ask Dr. Walsh to consider the third phase of his illness and the question of adrenal involvement. It is a rare finding to have *diabetes mellitus* and adrenal insufficiency. In the literature I think there are but 24 cases reported of Addison's disease and *diabetes mellitus*. The clinical picture in this patient is entirely opposed to these two diseases being associated. There is in the presence of these associated diseases a marked sensitivity to insulin and a constantly low blood sugar level. The blood sugar level in this patient was elevated on admission. Again the ketosteroid excretion is against a diagnosis of adrenal insufficiency, and the dosage of 53 units of insulin is a strong pointer against that diagnosis. We did not consider that he suffered from adrenal insufficiency for those reasons.

Three possible causes existed for his electrolytic pattern: (i) diabetes, (ii) liver insufficiency, (iii) adrenal insufficiency.

We considered diabetes to be the major factor, but were concerned about his hepatic state.

Another point of interest in this patient was his cardiac state. The patient died of heart failure, and did respond but minimally to treatment. Abnormal rhythms recurred constantly. There was no response to digitalis. This is the usual course of heart failure in hæmochromatosis—a failure of response to the usual therapeutic regimes. In Sheldon's monograph, he instances the rarity of this complication by noting that 10% of these patients die from heart failure and causes other than diabetes, liver failure and hepatic carcinoma. Actually the French literature is more aware of this condition, and they use the term endocrine to explain it. I agree with Dr. Walsh that there was interference with his intracellular enzymatic physiology, and believe this factor to be the basis of his irreversible heart failure rather than frank iron deposition in the muscle cells. An attractive theory is iron deposition in the vessel wall, as is used to explain the severe abdominal pain that occurs in these patients. In any case heart failure in hæmochromatosis is rare.

Another point of interest is that on reading the literature a short time ago, I was able to find but 30 cases of exogenous or transfusional hæmochromatosis. Thus it would appear that exogenous hæmochromatosis of this type is rare, and I think that this small number of recorded cases answers Dr. Walsh's question—is it worth while giving transfusions to subjects with refractory anæmia? By no means all patients with refractory anæmia will develop hæmochromatosis; they may develop hæmosiderosis. As would be expected, patients with refractory anæmia show impaired conversion of radioactive iron into hæmoglobin as compared with the normal 75% utilization in fourteen days of an intravenous test dose. Thus it would appear that the iron normally absorbed is being stored in these subjects. It has been shown in pernicious anæmia in remission and in polycythæmia that iron is readily absorbed, whilst in pernicious anæmia in relapse there is probably less iron absorbed. Iron absorption is therefore controlled, at least in these diseases, by the body's need for iron, and hence there probably exists some other factor in those refractory cases in which hæmochromatosis develops that increases the absorption of iron. This is one of the problems of this disease.

In conclusion, I would like to express my thanks to Dr. Walsh for his excellent discussion of this case.

DR. N. H. ROSE: Thank you, Dr. McGuinness. Are there any other clinicians, members of the pathology staff or visitors who would care to say something? Dr. Hirst.

DR. E. H. HIRST: First of all I should like to answer Dr. Walsh's question. I saw films of both the peripheral blood and the sternal marrow of this patient, and I was struck by the great difficulty in differentiating them from pernicious anæmia. There was everything to qualify for this diagnosis except the hæmoglobinized megaloblasts. In answer to his question as to whether it was persistently macrocytic, some of the reports in 1952 showed that it was normocytic or macrocytic, and always after splenectomy there were numerous normoblasts. A point has arisen out of this case which has puzzled me, and that is the absorption of iron in cases of anæmia. I do not understand iron absorption, but I know that some people follow the effect of intravenously administered iron in cases of hypochromic anæmia with persistently low mean corpuscular hæmoglobin concentration values by doing sternal aspiration, sectioning the small fragments of marrow, staining them by the Prussian Blue reaction and often finding iron deposited in the marrow. That iron, when it is granular, is called "hæmosiderin", and when it gives just a diffuse bluish cast to the cell is called ferritin. These people believe that since there is no other measure of the effective amount of iron given therapeutically, one should follow serial sections of the marrow in this way, and when free iron appears in the marrow it is the signal to stop giving iron. In this case, as Dr. Walsh has pointed out, the intake of iron is far in excess of that contributed by transfusions. It seems as he says, too, that something has gone wrong with absorption, so that the people are taking in increased amounts of iron. If one is dealing with any sort of anæmia in which the mere presence of anæmia or low hæmoglobin value or decreased oxygen saturation is going to cause an increased absorption of iron, then two questions arise: first of all, whether we should follow these cases with serial sectioning of the marrow, staining for iron, and stop iron therapy when stainable iron appears in the marrow; and secondly, whether there are any dietary measures which are effective in protecting the patient against the increased absorption of iron. I have come across several substances mentioned in the literature. One of them is phosphate, another is vitamin *K*, which is supposed to convert ferrous iron to ferric iron and make it less absorbable, and finally decrease in vitamin *C* intake. I would like to hear comments on this.

DR. PHYLLIS ANDERSON: I have one thought about the functional level of red cells in the blood. I know one patient who for many years has failed to get a red cell count of more than three and a half million, and he seems quite happy. Do we know at what level this patient might have managed to exist without transfusion, and could he have been ambulant and active at that level?

DR. N. H. ROSE: We will ask Dr. Walsh to answer some of these queries later.

Autopsy Report.

DR. A. A. PALMER presented the following report on an autopsy performed six hours after death.

The body was that of a well-nourished man. The skin had a pale grey tinge and in places there was brownish pigmentation. There was a left paramedian upper abdominal scar, and this scar was more heavily pigmented than the surrounding skin.

Pleural Cavities.—There were numerous adhesions in both pleural cavities.

Lungs.—The lower lobes of both lungs were congested.

Heart.—The heart was enlarged, weighing 17 ounces (normal 9·5 to 13·0 ounces). The cut surface of the myocardium was slightly redder than the normal. There were no valvular abnormalities. The coronary arteries showed some atheroma.

Liver.—The liver was greatly enlarged, weighing 126 ounces (normal 50 to 60 ounces). The lower edge extended 14·0 centimetres below the costal margin and had a conspicuous notch. The external and cut surfaces were reddish brown. There were thick fibrous adhesions on the surface of the left lobe, presumably resulting from the splenectomy.

Spleen.—The spleen had been removed (weight after removal was 15·5 ounces, normal 5 to 6 ounces).

Lymph Nodes.—Numerous slightly enlarged brownish paraaortic lymph nodes were found.

Adrenals.—The adrenals were of normal size.

Kidney.—A single horse-shoe kidney weighing 18 ounces (normal aggregate weight 10 to 12 ounces) was present. The parenchyma and pelves appeared normal.

Microscopic Examination.

Bone Marrow (Sternal).—The cellularity is within normal limits. Some lymphoid follicles with germinal centres are present. Hæmosiderin is fairly abundant.

Liver, Pancreas, Thyroid, Abdominal Lymph Nodes, Heart.—These organs contain large quantities of hæmosiderin. In the liver and pancreas there is also fibrosis, with proliferation of bile ducts in the increased portal connective tissue of the liver. Hæmosiderin is abundant in parenchymal as well as in connective tissue cells. The islet cells of the pancreas contain less pigment and show less evidence of damage than the acinar cells. In the heart hæmosiderin is abundant within muscle fibres. In some sections there is myocardial fibrosis, but this may be due, at least in part, to coronary atheroma, which sections show to be severe in places.

Kidneys, Adrenals.—These organs contain considerable amounts of hæmosiderin, especially the adrenals, where the concentration is greatest in the *zona glomerulosa*. In the kidney pigment is present chiefly in the distal convoluted tubules.

Voluntary Muscle (Psoas) and Skin.—Small amounts of hæmosiderin are present. In the skin the pigment is evident in and around sweat glands.

Spleen (Previously Removed at Operation).—Hæmosiderin is present in considerable amounts. There is some congestion. No evidence of extramedullary hæmopoiesis has been found. Only slight fibrosis is present.

Lung.—Chronic venous congestion consistent with cardiac failure.

Final Diagnosis.

1. Refractory anæmia associated with normally cellular marrow and splenomegaly.
2. Advanced exogenous hæmochromatosis with hepatic cirrhosis and pancreatic fibrosis associated with diabetes.
3. Cardiac hypertrophy and failure.

Conclusion.

DR. N. H. ROSE: Would you care to add any comments, Dr. Walsh?

DR. R. J. WALSH: In answer to Dr. Palmer, I have seen several cases of endogenous hæmochromatosis in which anæmia was present. This anæmia has disappeared when iron has been removed from the patient's circulation.

My other comments will be very brief. I think the lesson from this case is stated by Whitby. He feels that the risks attendant on splenectomy in good surgical hands are considerably less than the risks of a transfusion life, if a patient with refractory anæmia does not respond to treatment in a short time and if there is no evidence of extramedullary hæmopoiesis. He says, and I think it is sound advice, that he prefers to take a chance on splenectomy because most cases come to no harm and a few will be cured completely.

Another lesson, I think, is that iron therapy can be a bad thing. I am quite sure that iron therapy is given to an extraordinarily large number of patients when there is no justification for it. This is very bad medicine. Any patient with anæmia who does not respond to iron therapy, whose serum iron content rather than the marrow hæmosiderin content is high, should have the treatment suspended. If the serum iron content is high, there must be sufficient iron available. Once it becomes apparent that the anæmia is to be treated by transfusion only, then iron becomes positively dangerous. I am surprised at the number of patients receiving transfusions for refractory anæmia who are still being given iron by mouth or intravenously. The transfusion of blood itself provides more iron than one can hope to obtain by oral therapy.

DR. N. H. ROSE: By this discussion this afternoon you will all agree with me that Dr. Walsh has enhanced his already very high reputation, and I think you will also agree with me that we have never had a finer discussion and talk than we have had this afternoon. I should like to congratulate him again.

British Medical Association News.

VICTORIAN BRANCH NEWS.

Section of Preventive Medicine.

THE first meeting for this year of the section of preventive medicine of the Victorian Branch of the British Medical Association will be held in the Medical Society Hall, 426 Albert Street, East Melbourne, at 4.30 p.m. on Thursday, March 10, 1955. Dr. Kate Campbell will give an address entitled "The Prevention of Nursery Infections". All members of the Branch are invited to be present.

Public Health.

CONSULTATIVE COUNCIL ON MATERNAL MORTALITY IN VICTORIA.

THE following statement is published for the information of Victorian medical practitioners at the request of the Consultative Council on Maternal Mortality in Victoria:

The work of the Consultative Council on Maternal Mortality is greatly facilitated in cases in which a post-mortem examination has been made. In most cases in which no post-mortem examination has been made, it is usually due to the fact that the services of a pathologist are not available. When there has been a maternal death the Consultative Council on Maternal Mortality, with the approval of the Department of Health, has arranged that the services of Dr. K. M. Bowden, 12 Collins Street, Melbourne (telephone MF 4105), are available in a private capacity to make post-mortem examinations when the doctor in charge wishes such an examination to be made. This service will be rendered free of charge to the doctor or relatives. Permission from the relatives to carry out a post-mortem examination will be necessary before Dr. Bowden is asked to make the examination. Acting in this capacity, Dr. Bowden has no connexion with the coroner.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

GRATUITIES FOR MEDICAL OFFICERS ON EMIGRANT SHIPS.[1]

[Executive Council Minute Number 24, April 6, 1838.]

His Excellency the Governor laid before the Council an account presented by Mr. Wm. Rodgers Surgeon R.N. made by him for his service in selecting and conducting to this Colony, pursuant to the Instructions addressed to him by F. F. Elliott, Esq. Agent-General for Immigration dated 3rd July 1837, the emigrants who arrived on the 19th of January last by the ship Layton from Bristol, amounting in all to the sum of £535.4.11½ including £150 as a gratuity to which (in the terms of the usual instructions to surgeons on this Service) he becomes entitled if the "Government shall consider that he has satisfactorily performed the important duty entrusted to him".

His Excellency stated that on board this vessel no less than seventy children died on the voyage between England and New South Wales: and that although the vessel was reported free from disease on her arrival by Mr. Rodgers, and had consequently not been placed in quarantine, His Excellency had been informed that a malignant fever afterwards broke out among some of the passengers then resident on Mr. Wm. Macarthur's Estate at Camden. Under all which circumstances he felt it to be his duty to ask the advice of the Council as to whether he ought to authorize the payment to Mr. Rodgers of the gratuity claimed: for according to his Excellency's understanding of the term gratuity, it is something, the payment of which is contingent on the successful issue of the undertaking for which the gratuity is promised—and His Excellency requested the opinion of the Council as to whether they concurred in this view of the subject, in reference, in the first place to the particular case now before them.

The Council were of opinion that the proposed construction of the purport of that part of the "Instructions to Surgeons coming out in charge of emigrants", which relates to the allowance of a gratuity, does not appear to be in coincidence with the intentions of the Government, as hitherto understood, in making such an allowance, which seem to have had reference rather to the conduct of the Surgeons Superintendent, whether as meriting praise, for their general management of the emigrants, and for the propriety of their regulations for the preservation of cleanliness, ventilation, and good order, and their strictures in enforcing the same, or as deserving blame, for want of due attention to objects of such importance to the welfare of their charge—than to be dependent on the results, whether successful or otherwise. Although Mr. Rodgers has had the misfortune to lose the large number of children that has been mentioned, it is understood that they were chiefly very young; and that so far from any blame attaching to him for inattention to his duty, the propriety of his regulations for the preservation of good order, the evident control he possessed over the emigrants under his charge, their general cleanliness, and the good arrangements, and general comfort of their berths, excited the marked notice and praise of the Immigration Board when they visited the ship.

The Council are not in possession of sufficient information on the subject of the Fever said to have broken out among the passengers who went to Mr. Wm. Macarthur's Estates to enable them to form any opinion upon it: but under all the circumstances of Mr. Rodgers' case, in so far as the Council are at present informed, they are unanimously of opinion that payment of the full amount of the Gratuity claimed should be paid to him.

His Excellency then submitted for the opinion of the Council the general question, whether in future cases payment of the gratuity to surgeons in charge of Emigrants should be held to be contingent on the successful issue of their undertaking: on which it was decided by a majority of the Council that payment of the gratuity should not be held to be so contingent, but should be dependent on the good or bad conduct or endeavours of the claimant: but the same majority suggested that the regulations as to gratuities might be improved by assimilating them in some respects to the allowance of Head money made to Surgeons of Convict ships: which suggestion the council finally concurred in, advising the adoption of, with reservation to the Governor of the power of withholding the whole of the gratuity in established cases of bad conduct or neglect on the part of the Surgeons Superintendent: and further recommended to His Excellency the Governor that in every future case of Emigrants arriving in Vessels chartered by the Government, the now proposed mode of allowance of the Gratuity should be acted upon—and that notice to that effect should be given to the Surgeons in charge as early as practicable after their arrival.

[1] From the original in the Mitchell Library, Sydney.

Medical Practice.

THE USE OF ANTIBIOTICS.

THE Antibiotics Committee of the National Health and Medical Research Council has revised its table indicating the use of antibiotics in various diseases. It is published herewith at the request of the Director-General of Health, Commonwealth Department of Health, Canberra. Under the headings of the several antibiotic preparations the numbers 1, 2 and 3 refer to the preferences in order in which the drugs should be used, in other words which drug would be expected to provide most benefit in a particular illness.

NOTE: (*a*) Whenever possible, sensitivity tests should be carried out and the appropriate antibiotic used. (*b*) While combinations of some antibiotics are often useful as indicated in the work sheet, penicillin which is bactericidal should not

Number.	Disease.	Sulphonamides.	Penicillin.	Chlortetracycline ("Aureomycin").	Oxytetracycline ("Terramycin").	Tetracycline ("Achromycin" or "Tetracyn").	Chloramphenicol ("Chloromycetin").	Streptomycin.	Erythromycin.	Remarks.
1	Hæmolytic streptococcus (group A) infections.	—	1	2	2	2	—	—	3	Resistance to antibiotics not a problem. Use penicillin first. Most cases will respond.
2	*Streptococcus viridans* (endocarditis) infections.	—	1	3	3	3	—	1	2	Combined therapy: penicillin in large doses *plus* streptomycin in doses of two grammes per day up to a total of 20 grammes (adult).
3	*Streptococcus fæcalis* (endocarditis) infections.	—	1	2	2	2	—	1	2	Combined therapy as for number 2.
4	Puerperal infections ..	See remarks	1	2	2	2	—	—	3	Combined penicillin and sulphonamide therapy will control over 90% of all obstetrical infections. The others will usually respond to one of the tetracyclines. Sensitivity tests should be carried out.
5	Anaerobic streptococcal infections.	See remarks	1	2	2	2	—	—	3	
6	Pneumococcal infections ..	—	1	2	2	2	3	—	2	Resistance to antibiotics not a problem. Should respond to penicillin.
7	Meningococcal infections ..	1	1	2	3	2	3	—	2	Combined antibiotic and sulphonamide therapy.
8	Gonococcal infections ..	1	1	2	2	2	3	—	2	
9	Staphylococcal infections:									
	(*a*) In hospitals	—	2	1	1	1	2	3	See remarks	Resistance to antibiotics is a great problem, especially in hospitals, where sensitivity tests should be carried out. In general practice penicillin will be effective nearly always, but if there is no response in thirty-six hours other antibiotics should be tried. Sensitivity tests should be done if possible. Recent investigations have shown that 90% of staphylococcal infections in the newborn are penicillin resistant. See note (*d*) below in regard to erythromycin.
	(*b*) In general practice ..	—	1	2	2	2	3	3		
10	Brucellosis	See remarks	—	2	2	2	1	2	—	Combined antibiotic and sulphonamide therapy gives best results.
11	Pertussis	—	—	2	2	2	1	—	3	
12	Typhoid fever	—	—	2	2	2	1	—	—	
13	Influenzal meningitis ..	See remarks	—	2	—	2	1	1	—	Combined antibiotic and sulphonamide therapy with *Hæmophilus influenzæ* antiserum.
14	Urinary tract infections (uncomplicated):									Antibiotic resistance is a problem in this group. The occurrence of resistant strains follows no set pattern. In hospitals sensitivity tests should always be done. In general practice various antibiotics may have to be tried. Combinations may be found useful. Sulphonamides should be tried first. See notes (*e*) and (*f*) below on polymyxin and bacitracin.
	(*a*) *Escherichia coli* ..	See remarks	—	1	1	1	2	2	—	
	(*b*) *Kleisiella aerogenes* ..	See remarks	—	1	1	1	2	2	—	
	(*c*) *Proteus vulgaris* ..	See remarks	—	2	—	2	1	1	—	
	(*d*) *Pseudomonas pyocyanea*	See remarks	—	2	1	1	—	1	—	
	(*e*) *Streptococcus fæcalis* ..	See remarks	2	1	1	1	1	3	2	
15	Tuberculosis	—	—	—	—	—	—	1	—	Streptomycin should never be given alone. It is felt that in the first instance it is better to combine streptomycin with PAS keeping isoniazid in reserve. The preferred dose of streptomycin is one gramme twice weekly, except in acute cases, when one or two grammes daily may be given for a short period. See note (*h*) below in regard to viomycin.
16	Chancroid	—	—	1	—	2	—	—	—	
17	Friedlander bacillus (pneumonia).	—	—	1	1	1	2	1	—	
18	Salmonella infections (gastro-enteritis and bacteriæmia).	—	—	2	2	2	1	1	—	
19	Bacillary dysentery ..	1	—	2	2	2	2	2	—	
20	Plague	1	—	—	—	—	—	1	—	
21	Subacute bacterial endocarditis:									
	(*a*) *Streptococcus viridans* (see above).	—	1	3	3	3	—	1	2	Combined penicillin and streptomycin.
	(*b*) *Streptococcus fæcalis*	—	1	2	2	2	—	1	2	Combined penicillin and streptomycin.
	(*c*) *Hæmophilus influenzæ*	See remarks	—	2	—	2	1	1	—	Combined antibiotic and sulphonamide therapy.
22	Acute bacterial endocarditis:									
	(*a*) Staphylococcal ..	—	—	—	—	—	—	—	—	As above under number 7.
	(*b*) Other organisms ..	—	—	—	—	—	—	—	—	As above for corresponding organism.
23	Trachoma	1	—	2	—	2	—	—	—	
24	Surgical conditions of bowel (pre-operative and post-operative).	1	—	—	—	—	1	1	—	Combined antibiotic and sulphonamide therapy.
25	Pulmonary conditions (pre-operative and post-operative).	—	1	1	1	1	2	2	3	Depends on organism causing infection.
26	Typhus and other rickettsial diseases.	—	—	2	2	2	1	—	—	
27	Primary atypical pneumonia ..	—	—	1	1	1	—	—	—	
28	Psittacosis	—	—	1	2	1	—	—	—	
29	*Lymphogranuloma venereum*	—	2	1	1	1	3	—	—	
30	*Granuloma inguinale*	—	2	1	1	1	3	—	—	
31	Anthrax	—	1	2	2	2	—	—	—	
32	Syphilis	—	1	2	2	2	—	—	—	
33	Yaws	—	1	2	2	2	—	—	—	
34	Rat-bite fever:									
	(*a*) *Spirillum minus* ..	—	2	1	—	1	—	—	—	
	(*b*) *Streptobacillus moniliformis.*	—	—	—	—	—	—	1	—	
35	Tularæmia	—	—	1	1	1	—	1	—	
36	Gas gangrene	—	1	2	2	2	—	—	—	Combined with antiserum.

Number.	Disease.	Sulphonamides.	Penicillin.	Chlortetracycline ("Aureomycin").	Oxytetracycline ("Terramycin").	Tetracycline ("Achromycin" or "Tetracyn").	Chloramphenicol ("Chloromycetin").	Streptomycin.	Erythromycin.	Remarks.
37	Influenza	—	—	—	—	—	—	—	—	
38	Common cold	—	—	—	—	—	—	—	—	
39	Infectious mononucleosis	—	—	—	—	—	—	—	—	
40	Actinomycosis	See remarks	1	2	2	2	—	—	—	Penicillin should be given in large doses and may be combined with sulphadiazine. Tetracycline can be alternated with penicillin.
41	Acute amœbic dysentery	—	—	1	1	1	—	—	—	
42	Leptospirosis (Weil's disease)	—	1	2	—	2	—	—	—	
43	Diphtheria (see remarks)	—	1	2	2	2	—	—	—	Antiserum essential.
44	*Herpes zoster*	—	—	—	—	—	—	—	—	
45	Tetanus (see remarks)	—	1	2	2	2	—	—	—	Antiserum essential.

be given with the tetracyclines or chloramphenicol, as these antibiotics tend to interfere with the action of penicillin. (*c*) The importance of the development of antibiotic-resistant strains of organisms, especially in hospitals, is stressed. (*d*) Erythromycin ("Ilotycin", "Erythromycin") is effective chiefly against the Gram-positive cocci, its spectrum of activity being similar to that of penicillin. It has been shown that organisms will quickly develop resistance to erythromycin. No cross-resistance with other antibiotics has as yet been demonstrated. It is felt that the use of this antibiotic should be limited to the treatment of infections caused by organisms which are resistant to all other antibiotics. This restricted use will prolong the period of maximum value of this new antibiotic and should delay the appearance of resistant strains of organisms. (*e*) Polymyxin has not been included in the work sheet, as it is a highly toxic antibiotic and should be used only under careful supervision with the patient in hospital. Polymyxin is effective against some strains of *Pseudomonas pyocyanea*. (*f*) Bacitracin is not included in the worksheet, as the product at present available is suitable for local application only. (*g*) Neomycin, because of its toxicity, has not been included. Its usefulness for topical application in some conditions is recognized, however. (*h*) It is considered that viomycin in the recommended dose of two grammes twice a week is a safe antibiotic, as complications are relatively rare.

Correspondence.

YOUNG DOCTORS AND SPECIALIZATION.

SIR: I should like to thank Dr. Owen Green for commenting on certain points in my recent letter to THE MEDICAL JOURNAL OF AUSTRALIA and to make further observations on some of the issues he has raised.

Nobody will doubt that some years in general practice are desirable before entering a specialty, to increase the understanding of human frailties and to inform the future specialist thoroughly of general practice problems. Unfortunately, today, most surgical specialties call for many years of training overseas at a centre through which a high concentration of the right type of work passes. In no other way can one accumulate the extensive clinical and operative experience which must form the solid foundation of any surgical specialty. During this hospital training the future specialist must not ignore the ample opportunity to study patients as people. Otherwise he will emerge a poor specialist, and indeed, a poor doctor. This is equally true in general practice. Moreover, the introduction of the methods of other nations and the ideas of other men, experienced at first hand by young doctors training overseas, will always help to maintain a high medical standard in Australia and to prevent stagnation. Although most young men will do some general practice, it is obvious that the above training requires an early start.

That it is seldom possible to spend many years in general practice today before surgical specialization is unfortunate, but it is by no means the disaster claimed by Dr. Green and Dr. McIntosh. Who is to say that the consultants of Britain and America are inferior to those of Australia, or that our own senior consultants, who commenced their surgical training early, are inferior to their contemporaries who have a long background of general practice? Indeed, it is difficult to hear an opinion on this issue which is not highly coloured by a man's own experience.

If the supply of consultants exceeds the demand, as Dr. Owen Green claims, this is surely in the best interests of the profession. It leads to healthy competition, which must raise the standard of competence. Again, it provides a steady flow of specialists not only to teaching hospitals, as in the past, but to suburban hospitals and large country centres. Only when the demand exceeds the supply must we accept the mediocre.

Nor do many years in general practice entirely solve the early financial problems of the consultant. He must still face several lean years during study, training and early specialization, with less resilience, less willingness to accept a lower standard of living and heavier family commitments.

The hospital system in Britain which Dr. Green desribes as a "mess" does it less than justice. My own experience in English hospitals convinced me that perhaps the greatest general improvement in their health service since nationalization is in the standard of their hospitals (especially provincial) and in the standard of their consultant service. Dissatisfaction (chiefly financial) certainly exists amongst general practitioners and registrars isolated from their careers, but these anomalies are being gradually ironed out. It should be remembered that the health service in Britain is designed to serve needs very different from those of our own almost entirely middle-class population. It is therefore just as fallacious to judge their hospital service by our own standards as it is to compare the British general practitioner to the Australian general practitioner with his far wider practical scope.

Finally, we should not forget that our senior consultants of today, with their judgement matured by extensive experience over the years, were once younger men who had to adapt their training to the medical conditions of their day. Stimulated by the same interest and enthusiasm in his chosen field, there is no doubt that the young specialist of today will ultimately reach a similar high standard of competence.

Yours, etc.,

185 Macquarie Street,
Sydney,
February 2, 1955.

EWEN SUSSMAN.

SIR: May I reply to the letter of Dr. O. H. Green in THE MEDICAL JOURNAL OF AUSTRALIA, January 22, 1955.

"The reasonable man adapts himself to the world: the unreasonable one persists in trying to adapt the world to himself. Therefore all progress depends on the unreasonable man." (George Bernard Shaw.)

Similarly, Dr. Green would reason that all young specialists are unreasonable men in that they are endeavouring to make progress in medical science without a sound knowledge of general practice.

Does Dr. Green think that trainee jet pilots should spend years in the intensive study of the outdated planes of bygone years? We do not fight modern wars with bows and arrows for a similar reason. In other words the younger generation of specialists realizes that although it would be

very pleasant and informative to indulge in the "countless trivialities of everyday sickness", our life span is too short to allow undue time to be spent in the general field if a specialized field is their aim.

How can it benefit a surgeon performing an abdomino-perineal excision of the rectum to know how to deal with the domestic problems of Mrs. Jones? Just think of the many highly specialized fields such as plastic surgery, thoracic surgery, neurosurgery, urology and the like, which require many precious years of intensive study and practical training to equip the young specialist of today. How can he afford to give up additional years to general practice?

Most reasonable people would agree that the young specialist has a very arduous task in the competitive field of today. But no one would suggest that for this reason he should become a general practitioner and thus relinquish his earnest desires and specialist ambitions.

Dr. Green states: "Look at the mess that exists in England today with their hospital system." It is quite obvious that Dr. Green has little accurate knowledge of the system which he so trenchantly criticizes.

Having worked in English hospitals for a number of years, I can assure Dr. Green that the system is anything but a mess. The standard of medicine is extremely high. Patients are no longer reluctant to visit hospitals for specialized treatment. The English general practitioner is a good doctor although a busy one. He is doing an essential work, and he is the first to admit that his patients can now be assured of every benefit known to modern medical science.

Surgery, for example, is no longer dabbled in. It is performed by fully qualified and highly trained surgeons recognized by the National Health Service. The field of general practice in England remains a "specialist" field and always will.

The College of General Practitioners is receiving the support of specialists as well as general practitioners.

Medical progress exacts a penalty—time, and often coronary infarction. The modern cardio-vascular and neuro-surgeons must commence their training at an early age, whilst the heart remains bold, the hands strong and the brain alert.

In Australia we have the highest standard of general practice in the world, but it does not follow that our specialists must perforce spend years in general practice.

In the field of general medicine there is need for some attempt to gain general practice experience, but in the various surgical fields and the highly specialized medical fields valuable time would be lost.

We must recognize this changing age in its true light. Today is the age of rapid progress, intense competition, and time is precious. Let us, whether general practitioner or specialist, each to his chosen field with enthusiasm and a progressive outlook, untroubled by the pseudo-idealistic teaching some would have us heed. Let us make progress by adopting a more realistic approach to the specialist era, the jet era, the atomic era or what you will.

The young specialist recognizes certain defects in his armour, but knowledge in all fields is impossible today. His basic motives and aspirations remain good, and he endeavours to heed the lessons his forefathers have taught him.

William Osler once said when addressing the students of Yale University: "But each age has its own spirit and ideas, just as it has its own manners and pleasures. You are right to believe that yours is the best university at its best period."

I believe that we are living in a "specialist" world where, in the field of medicine, the general practitioner and the registered specialist have specific and specialized tasks to perform. Let us fulfil these tasks in a spirit of harmony and mutual respect.

Yours, etc.,

Brisbane,
January 26, 1955.

DANIEL LANE.

RUBELLA AND TUBERCULOSIS.

SIR: The article by Dr. Charles Engel entitled "Meeting of Diseases", which appeared in THE MEDICAL JOURNAL OF AUSTRALIA on January 15, 1955, page 72, reminded me of two cases in which patients suffering from pulmonary tuberculosis later contracted German measles. In each instance there was an acute flare-up of the pulmonary condition which ended eventually in death.

In this connexion, Clifford Allbutt (1897) in his now sadly neglected "System of Medicine" states that " . . . in those already suffering from some serious chronic disorder, such as tuberculosis, a fatal termination appears sometimes to be determined by an attack of rubella". It may well be, therefore, that not only the pregnant but also the tuberculous should avoid contact with rubella unless they have already suffered from the disease.

Perhaps this letter will stimulate others to record similar cases.

Yours, etc.,

175 North Terrace,
Adelaide,
January 26, 1955.

CHARLES SWAN.

Reference.

ALLBUTT, T. C. (1897), "A System of Medicine", 2:120. London: Macmillan and Company, Limited.

THE MANAGEMENT OF INDOLENT ULCERATION OF THE LEG.

SIR: The commendable article by Dr. Davis and Dr. Garlick on "The Management of Indolent Ulceration of the Leg" (M. J. AUSTRALIA, January 22, 1955) confirms that success follows treatment based on the work of Bisgaard—bandaging and exercises (to control venous stasis, lymph stasis and œdema), and massage (to soften areas of induration).

Curwen and Scott (1952),[1] formerly of St. Thomas's Hospital, London, report details of their application of Bisgaard's work with notable success in 427 cases followed over a four-year period.

In the interests of economy, of encouragement of home care and of prevention of recurrence, attention should be paid to Curwen and Scott's detailed description of the washable, elastic-reinforced, 80% non-absorbable bandages employed, as against "Elastoplast" stated to be used at present in the Brisbane Hospital practice described.

The principles of this, "The Ambulant Treatment of Complications Resulting from Varicose Veins and Allied Conditions", are few and simple. However, a personal knowledge of the proper methods and attention to detail are important to ensure the success of the methods.

The work is within the realm of the family doctor, and it might well be imparted to interested practitioners in a properly arranged series of regular post-graduate clinical demonstrations.

Yours, etc.,

Clayfield,
Brisbane,
January 29, 1955.

R. I. MEYERS.

THE POSSIBLE RELATIONSHIP OF LIPIDS TO ATHEROSCLEROSIS.

SIR: It seems a fair assumption that Sir Howard Florey's Halford Oration, with its crystal-clear reflections based on sound experimental data, will give added impetus to the above subject, the more so when it comes from a scientist who is lucky as well as great. A phase of special interest is his inclination to relate the Rokitansky-Duguid (thrombosis) with the lipid (imbibition) hypothesis, a concept in the United States of America I found to be very lightly entertained, though one pathologist of note did concede that "he thought Duguid had something".

At the meeting in Chicago last November on atherosclerosis considerable attention was given to the existence of an endogenous clearing factor in normal blood in direct relation to its lipoprotein content, and so it may be that we are expecting too much by way of structural change in the coronary vascular tree to explain the varying coronary syndromes. Is it, for example, rather a question of the amount of lipoprotein lipase, or endogenous clearing factor, or heparin co-factor, that determines why people die of coronary artery disease? As one who has chided the pathologist in this particular for not supplying the answer (McCristal, 1954), I tender my provisional apologies, with the reservation that this does not absolve him from establishing the frequency of the intimal hæmorrhage which by initiating spasm, mural thrombosis or bulging, *in vivo*, into

[1] *Ann. Phys. Med.* (1952), 1:17.

the lumen may cause myocardial infarction. At the moment the question for solution would appear to revolve around a team comprising a biochemist, biophysicist, pathologist, enzymologist and so on, with a cardiologist to direct at the clinical level.

With the tenor of doubt conveyed in the last paragraph it would seem idle to deplore the confusion that exists through the inability of many of the general medical population to reconcile a clinical impression with the electrocardiographic findings. This situation can be improved only through a better understanding of the underlying anatomic-pathologic-physiologic condition. In this particular one looks confidently to the dawn of a new era in the newly formed College of General Practitioners, which should be ideally composed to develop the standards of medical education merely commenced at graduation.

Coronary occlusion is now the number one killer of man at an age all too brief for him to reap the reward of a life well performed. The thought occurs that the College might organize throughout Australia, in cases either of death or recovery from unequivocal evidence of coronary occlusion, a *questionnaire* such as: age, sex, somatotype, family history, start of coronary attack and any relation to a fat meal. "Start" is used advisedly for the reason that premonitory signs may be concealed and arise in many instances from an intimal hæmorrhage which results hours or days later in myocardial infarction due to exacerbation from emotional or physical strain; and, with the current view of the role of heparin in lipid metabolism, a history of any related fat intake could be instructive. The value of any other items of information will not be laboured here.

Life insurance companies could and should be expected to assist in the above direction, since they are required not only to be concerned with the unpredictable coronary death, but also to explore and develop substandard insurance for the benefit of the community. Their calculations towards this end have, of necessity, to be based on refined prognoses and adequate statistical control.

Yours, etc.,

149 Macquarie Street, W. J. McCRISTAL.
Sydney,
January 31, 1955.

Reference.

McCRISTAL, W. J. (1954), "The Reason for Coronary Atheroma and Occlusion", M. J. AUSTRALIA; 1: 814.

THE MISUSE OF ANTIBIOTICS.

SIR: In support of R. Munro Ford (M. J. AUSTRALIA, January 29, 1955), might I relate the following? In recent weeks there came under my care a child who developed a pyogenic infection of the right external auditory canal, secondary to chickenpox. A pathological investigation revealed this organism to be sensitive to "Chloromycetin". This was duly given, and the child began to improve. The rapidity of improvement was not sufficient to suit the mother's convenience (school holidays—a cottage in the country). The opinion of an ear, nose and throat specialist was demanded: this "opinion" suggested penicillin. One injection only was given the child, and on the completion of this task the mother's comment to me was, "thank goodness at last something is being done". Another penicillin household.

I venture to offer the opinion that if the various antibiotic drugs were hung on lamp posts for selection by the public at large, then in a very short time there would be no penicillin left. Let us take the warning that we do not substitute the antibiotics for a correct diagnosis; that instead of being wonder drugs they become blunder drugs.

Yours, etc.,

Lane Cove, P. L. K. ADDISON.
New South Wales,
February 1, 1955.

THE MANAGEMENT OF EPILEPTIC CONVULSIONS.

SIR: Dr. V. H. Webster (January 15, 1955) states that in his experience paraldehyde is of little help in the control of infantile convulsions. At the Royal Alexandra Hospital for Children intramuscular paraldehyde has been the drug of choice in this condition for some years. During the past twelve months, some 150 infants have received paraldehyde by this route. I have found it a very effective and safe drug. Results are obtained some fifteen to thirty minutes earlier with paraldehyde than with soluble phenobarbitone.

I am in complete agreement with Dr. Webster when he condemns the antiquated, useless and very often dangerous "hot mustard bath". There is no scientific justification for this type of therapy.

I also make a plea for the cessation of the use of morphine as an anticonvulsant in infantile convulsions. It is a dangerous drug for these children, already suffering from respiratory difficulties, and it is not an effective anticonvulsant.

Yours, etc.,

The Institute of Child Health, WILFRED CARY.
Sydney,
January 24, 1955.

SOME CURRENT ANÆSTHETIC PROBLEMS.

SIR: I would like to thank Dr. G. R. Troup for his reply to my questions on current anæsthetic problems. Authoritative statements from experts like Dr. Troup are of great value to those whose duty it is to instruct succeeding groups of students.

Yours, etc.,

E. S. MEYERS.
The University of Queensland Medical School,
Brisbane,
February 2, 1955.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Annual Subscription Course: Programme for 1955.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that the following programme for 1955 has been arranged for the annual subscription course.

Dr. Richard A. Kern, M.D., Professor of Medicine and Head of the Department of Medicine, Temple University School of Medicine, Philadelphia, and Secretary-General of the American College of Physicians, who is well known for his work on allergy and geriatrics, will be visiting New South Wales from March 16 to April 6. Dr. Kern will give two lectures at the FOCLA course at Wollongong on March 17 and will be visiting Newcastle on the week-end of March 19-20. The lectures Dr. Kern will give in Sydney are as follows:

Friday, March 18, 1.15 p.m.: "The Principles of the Diagnosis and Treatment of Allergic Disorders", at the Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital.

Wednesday, March 30, 8.15 p.m.: "The Management of Respiratory Allergies, Including Status Asthmaticus", at the Stawell Hall, 145 Macquarie Street, Sydney.

Friday, April 1, 8.15 p.m.: "Drug Sensitivities, Notably Penicillin Reactions", at the Stawell Hall, 145 Macquarie Street, Sydney.

Monday, April 4, 8.15 p.m.: "The Clinical Application in General Practice of ACTH, Cortisone and Hydrocortisone", at the Stawell Hall, 145 Macquarie Street, Sydney.

Dr. Peter Kerley, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., President of the Faculty of Radiologists and Director of the X-Ray Department, Westminster Hospital, London, who will be visiting Sydney from March 20 to 28, will give the following lectures and demonstrations:

Tuesday, March 22, 8 p.m.: "Pulmonary Fibrosis", at the students' lecture room, Royal North Shore Hospital of Sydney.

Wednesday, March 23, 4 p.m.: "Tomography and Recent Diagnostic Developments in Thoracic Disease", followed by case demonstrations by the staff of the thoracic unit, at the students' lecture room, Royal North Shore Hospital of Sydney.

Thursday, March 24, 1.30 p.m.: clinico-pathological conference at the students' lecture room, Royal North Shore Hospital of Sydney.

Friday, March 25, 1.15 p.m.: "Pulmonary Changes in Congenital and Acquired Heart Disease", at the Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital.

Friday, March 25, 8.15 p.m.: "Benign and Malignant Tumours of the Lung", at the Stawell Hall, 145 Macquarie Street, Sydney. This lecture is being held in conjunction with the New South Wales Committee of the College of Radiologists of Australasia and the Australian Laennec Society.

Professor Joseph Stokes, Professor of Pædiatrics, Children's Hospital, Philadelphia, will be the Committee's official overseas lecturer for 1955, visiting Sydney about the first week of July. Details of Professor Stokes's programme are not yet complete, but will be announced shortly. During his visit to Sydney he will reside at the Royal Alexandra Hospital for Children.

Dr. McNair Scott, Director of Research, Children's Hospital, Philadelphia, will visit Sydney as Guest Professor to the Royal North Shore Hospital from August 15 to 20. He will be accompanied by his wife, Dr. Dwight Scott, who is also a research worker and a biochemist. Details of their programme will be announced later.

Sir Stanford Cade, K.B.E., C.B., F.R.C.S., M.R.C.P., Senior Surgeon, Westminster Hospital, London, Member of the Council of the Royal College of Surgeons of England and Member of the Cancer and Radiotherapy Committee of the Ministry of Health, will be visiting Sydney during August at the invitation of the Post-Graduate Committee. Sir Stanford Cade is a noted authority on the surgery of cancer. It is expected that his visit will be for four weeks, the last week of which will coincide with the meeting of Congress, at which he will participate in a plenary session on cancer. It is possible that he may be accompanied by Professor Brian Windeyer, Director of the Meyerstein Institute of Radiotherapy, Middlesex Hospital, London.

It is expected that Professor Robert Platt, M.Sc., M.D., F.R.C.P., Professor of Medicine in the University of Manchester, and Physician, Manchester Royal Infirmary, will visit Australia later in the year.

Also, it is expected that Dr. W. S. C. Copeman, O.B.E., of West London Hospital, and Chairman of the Empire Rheumatism Council, will be visiting Sydney about September or October.

The annual subscription course covers attendance at lectures by overseas lecturers and other specially arranged activities. The annual fee is £2 2s. from July 1. The fee for resident medical officers is £1 1s. A diary card, setting out details of lectures arranged, is forwarded to members throughout the year. Occasionally last-minute alterations to meetings are necessary, and these are notified by advertisement in *The Sydney Morning Herald* ("Public Lectures") if possible on the day before the meeting. Further particulars may be obtained on application to the Course Secretary, The Post-Graduate Committee in Medicine in the University of Sydney, 131 Macquarie Street, Sydney. Telephones: BU 4497-8. Telegraphic address: "Postgrad, Sydney."

Conference on Graduate and Post-Graduate Education.

The Post-Graduate Committee in Medicine in the University of Sydney announces that it proposes to hold the second conference on graduate and post-graduate medical education in the Stawell Hall, 145 Macquarie Street, Sydney, at 8 p.m. on Wednesday, March 2, 1955. The subject of this conference will be "The Training of Specialists".

Attendance will be by invitation, and all bodies wishing to be represented, or persons wishing to attend this conference, should communicate as soon as possible with the Post-Graduate Committee in Medicine in the University of Sydney, 131 Macquarie Street, Sydney (BU 4497).

POST-GRADUATE COMMITTEE IN MEDICINE OF THE UNIVERSITY OF ADELAIDE.

PROGRAMME FOR 1955.

THE Post-Graduate Committee in Medicine of the University of Adelaide announces the following programme for 1955.

Courses for Higher Degrees.

Medicine.—Provided there are sufficient applicants, there will be a three months' full-time course suitable for M.R.A.C.P. candidates, beginning in May. It will include all branches in which candidates will be examined. Prospective applicants may obtain details from the Medical Secretary.

Surgery.—Provided there are sufficient applicants, there will be a comprehensive course in anatomy, physiology and pathology suitable for F.R.A.C.S. I candidates, beginning in June, in preparation for the examination in September.

Other Diplomas.—The Committee wishes to notify graduates that facilities can be arranged for those wishing to study for higher degrees in radiology or for the D.P.M. Courses in preparation for examination for diplomas in other specialties can be arranged for individuals or small groups. Where this is impracticable in South Australia, information on facilities for training interstate can be obtained from this office.

Courses for General Practitioners.

Refresher Week.—A refresher week will be held from May 30 to June 3, 1955.

Medicine.—Ward rounds will be held every Wednesday afternoon at 4.30 p.m. from March 2 to November 2. The card listing the tutors will be circulated shortly.

Surgery.—For practitioners wishing to undertake further training in surgery the Committee will be glad to arrange programmes to suit individual requirements. Training can be arranged for any period ranging from a few hours any day of the week to an indefinite term. The period from 6 to 11 p.m. is always busy with emergency surgery at the Royal Adelaide Hospital and may suit certain practitioners. A continuous term of one or more weeks has been found satisfactory to graduates in the past. Any interested graduates are asked to contact the Medical Secretary.

Obstetrics.—A course of obstetric tutorials for general practitioners will begin on March 1. Tutorials will be given at 4 p.m. every Tuesday afternoon for ten weeks at the Queen Victoria Maternity Hospital or the Queen Elizabeth Hospital. A detailed programme may be obtained from this office. Numbers will be limited.

Country Courses.—Further week-end courses will be arranged at the request of country medical associations. Details of these courses will be advertised at a later date.

Edward Stirling Lecturer.

Dr. R. Kaye Scott, F.R.A.C.S., F.F.R., D.T.R.E., of Melbourne, has consented to deliver the Edward Stirling Lectures in 1955. They will be given in the Verco Theatre on Tuesday, May 31, and Thursday, June 2.

Overseas Lecturers, 1955.

The Post-Graduate Federation has arranged for Professor Joseph Stokes, Professor of Pædiatrics, Children's Hospital, Philadelphia, United States of America, to visit Australia as the official overseas lecturer for 1955. He will be in Adelaide during the first week in August.

Dr. Peter Kerley, M.D., F.R.C.P., F.F.R., Director of the X-Ray Department, Westminster Hospital, London, will lecture in the Verco Theatre at 8 p.m. on Thursday, March 10, on the subject "Lung Changes in Congenital and Acquired Heart Disease". Dr. Kerley will address a meeting of the College of Radiologists, to which members of the profession are invited, in the Verco Theatre at 8 p.m. on Monday, March 14, on the subject "Pulmonary Fibrosis". Dr. Kerley will also attend clinical meetings at the Royal Adelaide Hospital and Adelaide Children's Hospital.

Dr. John Gillies, F.R.C.S., M.R.C.P., Consultant Anæsthetist, of the Royal Infirmary, Edinburgh, will lecture in the Verco Theatre at 8 p.m. on Tuesday, March 15, on the subject "New Trends in Anæsthetic Practice".

Professor R. A. Kern, Professor of Medicine, Temple University, Philadelphia, will lecture in the Verco Theatre at 8 p.m. on Tuesday, March 22, on the subject "Principles of Diagnosis and Treatment of Allergic Disorders".

In addition to the above, negotiations are proceeding to arrange lectures by the following eminent ophthalmologists, both of whom are expected to visit Australia in October, 1955: Dr. Norman Ashton, Director of the Department of Pathology, Institute of Ophthalmology, University of London, and Professor Pauffique, of Lyons, France.

Post-Graduate Study in the United Kingdom.

The Post-Graduate Committee wishes to advise graduates intending to undertake post-graduate training overseas that information is available from this office concerning courses and facilities in the United Kingdom. If desired, the Committee will arrange courses and introductions through the cooperation of the British Post-Graduate Medical Federation

and other post-graduate organizations in the United Kingdom.

Fees for Lectures and Courses.

The fees for annual tickets for lectures and courses are £3 3s. These cover admission to all lectures by overseas and interstate lecturers. Admission to individual lectures is by payment of 15s. at the door.

The fees for comprehensive tickets are £10 10s. These cover admission to all overseas and interstate lectures, medical ward rounds, obstetric tutorials, refresher week, and one week or any twelve selected lectures in a higher degree course.

The fees for the refresher week are £3 3s., for the obstetric tutorials £3 3s., for the M.R.A.C.P. course £31 10s., and for the F.R.A.C.S. I course (June) £31 10s.

Further information may be obtained from the Secretary (telephone: W 3211).

Enrolments.

In all cases, application for enrolment in post-graduate courses should be made to the Medical Secretary as soon as possible.

Obituary.

GUSTAV BONDY.

WE have received from Dr. Eric P. Blashki the following appreciation of the late Dr. Gustav Bondy.

Dr. Gustav Bondy died at Sydney on December 20, 1954, at the age of fifty-four years. He was an otologist of

distinction and belonged to the "grand days" of the Vienna School, having been assistant at the time of Politzer and Urbantschitsch, as well as a colleague of Barany.

Bondy's special study was the development and anatomy of the middle ear, especially Shrapnell's membrane and the attic. He described the conservative type of radical mastoid operation, which is usually known as Bondy's operation. For many years he had been a university lecturer and surgeon in charge of the otological department of the *Krankenhaus Wieden*, in Vienna, where he taught many American and several Australian graduates.

Driven from his post by the Nazis and personally in danger, he came to Sydney in 1939 and was shortly registered to practise by virtue of the recognition of his personal eminence in his specialty. From that time until last year he carried on his work quietly until failing health compelled him, unwillingly, to stop.

Personally Bondy was a man of sunny disposition and great charm. He was a gentle soul and possessed artistic ability of a high order. He had a good and wide knowledge of music and was an able pianist. He also was a very good amateur photographer, and his pictures were remarkable not only for the taste displayed but for the appreciation of composition.

Since his arrival in Australia his retiring nature kept him from all public occasions, and he did not take any active part in professional gatherings. Nevertheless, he did gather a large circle of new and very firm friends and admirers, and these will join in sympathy with Mrs. Bondy and his twin sons, who survive him.

MORDAUNT GRAHAM SUTTON.

DR. MORDAUNT GRAHAM SUTTON, who was born at Beenleigh, Queensland, in 1890, was a son of Dr. Alfred Sutton, a Guy's Hospital graduate who practised at Beenleigh after migrating from England. He was educated at the Brisbane Grammar School and later at St. Andrew's College in the University of Sydney. He graduated in 1914, and after a short term of residency at the Brisbane Hospital he enlisted in the Australian Army Medical Corps and went overseas to serve as a medical officer in the first World War. He saw most of his service with the Second Field Ambulance and attained the rank of major. On demobilization he studied in London and Edinburgh and passed his examination for F.R.C.S., Edinburgh, in 1919.

Before returning home Graham Sutton married Beryl Southgate, of London, who predeceased him by two years. On his return to Brisbane he undertook general practice at South Brisbane. He soon became interested in gynæcology and urology and was appointed honorary surgeon to the Lady Lamington Hospital for Women. He was admitted as a Fellow of the Royal Australasian College of Surgeons in 1930, whereupon he gave up general practice and devoted himself entirely to urology. However, he always considered that female urology was closely associated with gynæcology, which he continued to practise. On the merging of the Lady Lamington Hospital with the Brisbane Hospital he became honorary urologist on the staff and was also consulting urologist to the Hospital for Sick Children. On reorganization of the hospital staff in 1938 he became a senior part-time urologist and held this position until his retirement in 1950.

After serving on the Council of the Queensland Branch of the British Medical Association for a number of years, Graham Sutton was elected President for the year 1936 and thereafter was a member of the ethics committee. He was frequently called on for advice in respect to building alterations, in which matters he had much knowledge. He was remarkably skilled with his hands and had a well-fitted workshop in the basement of his house. There he made many instruments and appliances, such as those required for the performance of Millen's retropubic prostatectomy, an operation which he pioneered in Brisbane. During the second World War he designed and constructed a mechanical plaster-bandage machine, which did valuable service in turning out thousands of these bandages for the hospital use during the years when they had otherwise to be made by hand.

Although during his school and university days he played football and subsequently tennis, his main hobby in later years was his mechanical work, and he personally rebuilt a holiday house at Tamborine Mountain, a job he completed during the years immediately preceding his death. He is survived by his two sons, Kenneth and Peter.

DR. F. W. R. LUKIN writes: Despite his service in the interests of the profession, Graham Sutton was not as intimately known to the individual members as his talents warranted, and this was because he was of a retiring and

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JANUARY 22, 1955.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	3(2)	1	8(4)	..	..	..	..	..	12
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	2(1)	..	..	..	..	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	1(1)	..	..	..	1
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	..	15(10)	4(1)	..	4(3)	..	..	..	23
Diphtheria	2	5(4)	2(2)	1(1)	8(8)	..	..	..	18
Dysentery (Bacillary)	..	4(3)	10(9)	1	8(6)	..	..	..	23
Encephalitis	..	3(3)	..	2(1)	..	..	..	..	5
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	64(35)	73(58)	..	8(1)	4(1)	1	2	3	155
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	1(1)	..	..	..	..	..	1
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	1(1)	3	2	..	..	1(1)	1	..	8
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	11(1)	6(3)	10(5)	4(4)	..	1(1)	..	..	32
Puerperal Fever	..	..	3	1	..	..	..	..	4
Rubella	..	27(15)	1(1)	..	12(6)	..	..	..	40
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	4(2)	13(6)	2	2(2)	3	1	..	..	25
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1	..	..	..	..	..	1
Trachoma	..	..	..	..	3	..	..	..	3
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	52(42)	27(18)	15(1)	5(3)	5	4(1)	2	..	110
Typhoid Fever	..	..	..	..	1(1)	..	..	..	1
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JANUARY 29, 1955.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania	Northern Territory.[3]	Australian Capital Territory.	Australia.[3]
Acute Rheumatism	3(2)	3(3)	3(1)	..	..	..	..	..	9
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	3	..	..	..	..	..	..	..	3
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	8(7)	7(7)	4(3)	..	..	..	..	..	19
Diphtheria	4(4)	..	..	..	15(14)	..	..	..	19
Dysentery (Bacillary)	..	2(2)	9(9)	..	2(2)	..	..	..	13
Encephalitis	..	2(1)	..	..	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	1(1)	..	..	..	..	..	..	1
Infective Hepatitis	47(21)	55(40)	..	6(4)	2	..	..	1	111
Lead Poisoning	..	..	1	..	..	..	..	..	1
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	..	..	..	..	..	..	..
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	3(1)	3(1)	2	..	..	..	..	..	8
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	3(1)	14(6)	13(5)	..	..	1	..	..	31
Puerperal Fever	..	..	3	..	..	..	..	..	3
Rubella	..	20(17)	..	1	13(11)	1	..	..	35
Salmonella Infection	..	..	..	..	17(1)	..	..	..	17
Scarlet Fever	7(5)	8(6)	1(1)	2(2)	..	1	..	..	19
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	2(2)	..	1	..	..	..	..	3
Trachoma	..	..	..	..	8	..	..	..	8
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	43(36)	15(11)	15(2)	12(8)	10(10)	4(2)	..	..	105
Typhoid Fever	..	..	..	..	1	..	..	..	1
Typhus (Flea-, Mite- and Tick-borne)	..	..	2	..	..	..	..	..	2
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from Northern Territory.

placid temperament. He sought not renown but rather knowledge and pursued perfection in the activities which interested him. Consequently he made less than the usual number of close friends, but to these he gave generously his assistance and affection. An atmosphere of calm confidence and unhurried deliberation accompanied him, and of this his patients and colleagues were conscious. A tendency to unpunctuality was more than compensated for by the charm of his personality, and no theatre sister could ever reprove him. The quality of his work made him a welcome visitor in every hospital, and his patients always felt with good reason that they were getting constant thorough and skilled attention. Towards the happiness of many his contribution was great.

Research.

NUFFIELD FOUNDATION AUSTRALIAN ADVISORY COMMITTEE.

THE Chairman of the Nuffield Foundation Australian Advisory Committee, Sir John Medley, announces that Nuffield Foundation Dominion Travelling Fellowships have been awarded to the following Australian graduates:

Dr. R. A. Joske, of Melbourne, who since 1953 has been Associate Assistant to the Head of the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research in Melbourne, has been awarded a Fellowship in Medicine. Dr. Joske will spend a year in the Professorial Medical Unit, University College Hospital, London, under Professor M. Rosenheim, studying chiefly renal disease and hypertension.

Dr. G. M. Kellerman, of Sydney, has been awarded a Fellowship in Medicine. Dr. Kellerman hopes to work under the direction of Professor C. H. Gray at the King's College Hospital Medical School, where work is being carried out on the effects of salt deficiency on electrolyte distribution throughout the body.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 3, of January 13, 1955.

ROYAL AUSTRALIAN AIR FORCE.

Permanent Air Force: Medical Branch.

The following Squadron Leaders (Acting Wing Commanders) are promoted to the rank of Wing Commander: J. B. Craig (05799), L. R. Trudinger (033059), M. C. Clarke (011321).

The following Flight Lieutenants are promoted to the rank of Squadron Leader: R. G. Sharp (023027) (Acting Squadron Leader), D. B. Heylan (023063) (Acting Squadron Leader), K. M. Woods (023095) (Acting Squadron Leader), T. F. Sandeman (035954), R. H. B. Sacks (036080) (Acting Squadron Leader), P. A. O'Brien (035952) (Acting Squadron Leader), J. McC. Morrison (036133) (Acting Squadron Leader).

Nominations and Elections.

THE undermentioned has applied for election as a member of the South Australian Branch of the British Medical Association:

Hronsky, Eugenia, qualified 1954 (Univ. Adelaide), 71 Queen Street, Norwood, South Australia.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Barbour, Robert Angus, qualified 1954 (Univ. Adelaide); Branson, Dean Martin, qualified 1954 (Univ. Adelaide); Brummitt, Robert, qualified 1954 (Univ. Adelaide); Bodmer, Noel Frederick John, qualified 1954 (Univ. Adelaide); Handley, Joan Marie, qualified 1954 (Univ. Adelaide); Hobbs, Graham Alan, qualified 1954 (Univ. Adelaide); Kearney, Margaret Patricia, qualified 1954 (Univ. Adelaide); Lawson, Margaret Leaine, qualified 1954 (Univ. Adelaide); Munday, Robert Neill, qualified 1954 (Univ. Adelaide); Mauger, Alan Harris, qualified 1954 (Univ. Adelaide); Nurrell, Helen Calvert, qualified 1954 (Univ. Adelaide); Pak-Poy, Reginald Kenneth Felix, qualified 1954 (Univ. Adelaide); Playford, Margaret Claire, qualified 1954 (Univ. Adelaide); Preston, John Arthur Rowland, qualified 1954 (Univ. Adelaide); Steele, David Macdonald, qualified 1954 (Univ. Adelaide); Webling, Donald D'arcy, qualified 1954 (Univ. Adelaide); Fuller, Clarence Oliver, M.B., B.S., 1954 (Univ. Adelaide) (qualified 1953); Jessup, Leonard Clive, M.B., B.S., 1952 (Univ. Adelaide).

Deaths.

THE following death has been announced:

WALKER.—Eric Lorimer Walker, on January 27, 1955, at Brisbane.

Diary for the Month.

FEB. 14.—Victorian Branch, B.M.A.: Finance Subcommittee.
FEB. 15.—New South Wales Branch, B.M.A.: Medical Politics Committee.
FEB. 16.—Victorian Branch, B.M.A.: Branch Meeting.
FEB. 17.—Victorian Branch, B.M.A.: Executive of Branch Council.
FEB. 22.—New South Wales Branch, B.M.A.: Ethics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all contract practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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